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FOREWORD

MEREDITH CAMPBELL, M.D.

The widening appreciation of the clinical importance of urologic disease in the young reflects both the technological (instrumental, radiographic, chemotherapeutic) advances in this field and the enlightened medical school teaching of the past 25 years. Instead of the rare instance three decades ago, many thousands of infants and children throughout the world are today given the benefit of adequate urologic study and modern urosurgical treatment. Much of the diagnostic evidence thus gathered and the records of therapeutic achievements are finding their ways to the printed page. Uropediatric articles and reports in the current urologic and pediatric periodicals of 30 years ago accounted for less than 2 per cent of the total contents, while now in the *Journal of Urology*, for example, approximately one in five articles is concerned with some phase of urology in the young. A similar but somewhat less striking increase is likewise noted in the special pediatric journals both here and abroad.

The opportunities and need for further advances as well as technical research in this field are still enormous. Untold thousands of infants and children are in need of urologic care. It seems likely that our splendid miniature cystoscopic instrumentarium of today will be further improved upon. On an average of once a month some new and promising antibiotic or drug of special effect on the urinary tract is announced. Since about one in every eight newborn infants has some urogenital tract maldevelopment, major or minor, and often more than one anomaly, the need for greater clinical consciousness in this field is evident. The physician must be cognizant of the potential destructive uropathy and symptomatic picture(s) which often result from these congenital lesions.

Today the field of urology in children is insufficiently regarded to encourage one to devote his entire practice to it even in large cities.

Nevertheless, with wider education of the medical profession and an increased awareness of the laity as to what can be accomplished when the patient is an infant or child, I foresee the time—perhaps ten years away—when the demand for top-grade practitioners, well grounded and experienced in general urology and especially trained in uropediatrics, will encourage them to devote full time to pediatric urology just as some physicians do now to pediatric otolaryngology, pediatric psychology, pediatric dentistry and pediatric surgery.

This symposium is intended not only to present the reader with concise practical evaluation of the more usual uropediatric problems, but also to suggest therapy. It is hoped that the pediatrician or the general practitioner with a uropediatric problem will be dispelled of the notion that the child should always be rushed off to the urologist at once. There is much of genuine interest that the nonurologist can and should do, and there is real help he can give if he will, especially in the initial, fundamental study of the patient. This includes, in addition to a comprehensive history taking and thorough physical examination, urinalysis and bacteriologic study of the properly collected urine specimen, a satisfactory preliminary excretory urographic study, estimation of the renal function (phenolsulfonphthalein excretion test, blood nitrogen level, and so on), determination of residual urine, rectal examination, and so forth. Moreover, I strongly suggest that pediatricians should be able and willing to perform meatotomy when it is indicated, and to gently dilate the anterior urethra with sounds if necessary. Cystoscopy and allied procedures had best be delegated to a properly qualified and gentle instrumenteur. Finally, and it cannot be too forcibly emphasized, *a tender age should never be accepted as a contraindication to adequate urologic study when cogent reasons for such an examination exist.* It is surprising how often in the technical instrumental investigation of so-called medical nephritis an important nonrenal uropathy will be disclosed as the underlying lesion. Especially is this so in congenital ureteral and bladder neck obstructions; with their eradication the albuminuria, casts and other evidence of "Bright's disease" disappear.

My sincere gratitude to the eminent contributors who have so generously given of their talent, experience and time to make this volume both a practical and an authoritative source.

INDICATIONS FOR UROLOGIC EXAMINATION IN CHILDREN

MEREDITH CAMPBELL, M.D.

Urologic examination of infants and children has now become a worldwide daily procedure. The vast range of uropathy thus revealed—chiefly congenital and often grave—and the demonstrated therapeutic benefits made possible by accurate diagnosis have aroused wide and justifiable enthusiasm, particularly among the younger generation of pediatricians and urologists. Yet only a small portion of the children deserving of adequate investigation are fortunate enough to receive it, and even now thousands of young patients are urologic cripples or are dying of a curable urologic disease simply because of the ignorance or the temerity of their medical advisors who fail to seek special urologic aid for the establishment of the correct diagnosis and the treatment of these children.

Thirty years ago, when I became acutely interested in this field of study, instrumental urologic examination of children was still a novelty; these young patients were hesitatingly subjected to urologic investigation only when they presented a renal or vesical mass, suffered pain attributable to obvious urinary tract disease, or had persistent hematuria. As the horizons and volume of these studies have broadened, it has been convincingly demonstrated that urologic disease is extremely commonplace in the young, particularly the obstructive and/or persistent infection varieties. In fact, about 90 per cent of the main urologic problems in the young are due to urinary blockage or infection, or both, most of the obstructing lesions being congenital. About 12 per cent, or one in eight, of all newborn children show some anomalous development in the urogenital tract, a high incidence well recognized by pathologists with extensive experience in autopsy examinations of the young, but little dreamed of by practicing clinicians with the exception of a few pediatricians and urologists who have extensively studied uropathy in this age group.

Many conditions previously considered strictly medical and most com-

monly diagnosed as nephritis have been found to be caused by surgical renal lesions with failing renal function, but due to remedial urinary obstruction, infection or both. Examples of this are persistent gastrointestinal disturbances, which are present in at least half of all cases of advanced uropathy, in some cases of hypertensive vascular disease, in growth retardation, and in the clinical syndrome of osteitis fibrosa cystica, which is frequently designated as renal rickets or secondary renal hyperparathyroidism.

During the past 30 years continuing efforts to reduce the caliber and improve the visual field of miniature cystoscopes have developed a wide variety of instruments now used all over the world. Today complete urologic examination and treatment can be carried out in the newborn male in a manner comparable in every way to that done when the patient is an adult. Resectoscopes, electrocutting and grasping instruments and miniature operating cystoscopes enable us to perform transurethral or endoscopic maneuvers rather than open surgical procedures.

The advent of excretory urography 25 years ago did much to facilitate urologic diagnosis in the young, but here the extremely small caliber of the urinary channels to be demonstrated, together with often exasperating radiographic technical dfficulties, greatly diminishes the diagnostic effectiveness of the method in infants, in whom satisfactory radiographic studies are obtained in only half of the cases. In older children the excretory urographic investigation is of somewhat greater value. It is my practice in nearly every case to have an excretory urographic study made prior to cystoscopic examination and only for the diagnostic clues or preliminary evidence it may disclose, e.g., unsuspected hydronephrosis, ureteral reduplication, ureteral obstruction, stone in the upper urinary tract, foreign body in the bladder, and so forth. Yet the best excretory pyelograms in the young are not nearly as definitive as properly made retrograde pyelograms which I make in nearly all cystoscopic studies and practically always bilaterally.

Experience has demonstrated that children of all ages withstand complete urologic investigation far better than their elders and with fewer reactions. No child should be permitted to harbor undiagnosed urologic disease or be denied the benefits of urologic study and care simply because of fear of unfortuitous reaction. In my experience the child's parents regularly prove more cooperative than the child's physician uninformed in urologic problems.

INDICATIONS FOR UROLOGIC INVESTIGATION

These are based on the urologic symptoms or clinical manifestations which the patient exhibits; these symptomatic syndromes are discussed here most briefly, and in the following order:

1. Pyuria
   a. Acute persistent
   b. Chronic
2. Frequency of urination—dysuria, frequency, urgency, etc.
3. Hematuria (except acute nephritis)
4. Abdominal pain
5. Abdominal tumor
6. Anomaly of the external genitalia
7. Urogenital injury
8. Spinal cord injury and disease
9. Enuresis
10. Renal insufficiency
11. Retarded growth
12. Hypertensive vascular disease

Pyuria

By definition this is pus in the urine, and almost always signifies infection in the urinary tract. Pyuria is the commonest indication for urologic examination in children. In rare instances leukocytes exist in the urine in the absence of demonstrable infection (amicrobic pyuria), a condition which may result from nonbacterial congestion, obstruction, calculous disease, trauma or virus infection. The potential direct and indirect causes of pyuria are numerous; the more frequent are schematically indicated in Figure 1. In my experience pyuria in the newborn occurs more often in males.

Pyuria is correctly identified by microscopic examination of a properly collected urine specimen; in females of all ages this collection should be by aseptic catheterization under visualization after having cleansed the external genitalia and introitus with an antiseptic solution such as mercury oxycyanide or mercury bichloride 1:1000. Amazingly, the majority of physicians still fail to recognize that the voided urine from a female is worthless for the accurate identification of either the specific bacterial invader(s) or the amount of pyuria present. I have not submitted a voided specimen from a female for urinalysis in 35 years. Though the commonly practiced scrubbing of the labia and introitus may largely eliminate cellular contamination of the voided specimen, even this is uncertain, and it does nothing to eliminate secondary urinary contamination by labial bacteria.

In the male satisfactory specimens for urine culture can be obtained by urination after first retracting the prepuce, cleansing the glans and separated meatus with an antiseptic solution such as previously described. The patient now voids, and, after a few cubic centimeters of urine have been passed, the sterile collecting vessel is introduced into the stream to collect the specimen. Unless this technique can accurately be followed, do catheterization in the male. These methods should also be used for collecting the urine when hematuria is under investigation.

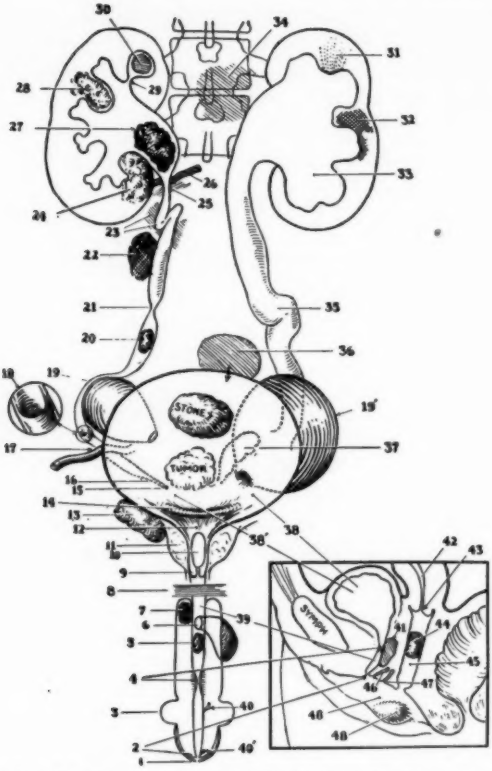

Fig. 1. Direct and indirect causes of pyuria: 1, stenosis of prepuce; 2, stenosis of urethral meatus and so forth; 3, paraphimosis; 4, urethral stricture; 5, urethral stone; 6, urethral diverticulum; 7, periurethritis, periurethral abscess; 8, cowperitis, chronic external sphincterospasm; 9, congenital valves of posterior urethra; 10, hypertrophy of verumontanum, verumontanitis, enlarged utricle or utricular diverticulum; 11, prostatitis, prostatic abscess; 12, contracted neck of bladder, median bar; 13, periprostatitis or pelvic suppuration; 14, mucosal fold at outlet of bladder, trigonal curtain; 15, stricture of ureteral meatus, ureterocele; 16, stricture of ureterovesical junction; 17, vascular obstruction of lower part of ureter; 18, congenital ureteral valves; 19, ureteral obstruction by compression from diverticulum; 19′, diverticulum; 20, ureteral stone; 21, ureteral stricture; 22, periureteritis, periureteral phlegmon or abscess; 23, ureteral kink, periureteral fibrous bands; 24, renal tumor; 25, stricture of ureteropelvic junction; 26, aberrant vessel (obstruction of upper part of ureter); 27, pelvic stone; 28, renal tuberculosis; 29, stricture of calyceal outlet; 30, calyceal stone; 31, pyelonephritis; 32, pyonephrosis; 33, "pyelitis," infected hydronephrosis; 34, perirenal suppuration invading urinary tract, spinal disease (Pott's disease and so forth); 35, hydroureter; 36, pericystic abscess rupturing into bladder; 37, seminal vesiculitis; 38, neuromuscular vesical disease; 38′, cystitis; 39, urethritis; 40, folliculitis (Littre); 40′, folliculitis (Morgagni); 41, periurethritis, periurethral abscess; 42, endometritis; 43, cervicitis; 44, foreign body in vagina; 45, vaginitis, hydrocolpos, fusion of labia minora; 46, skenitis; 47, folliculitis of introitus; 48, bartholinitis. (From Campbell: Clinical Pediatric Urology.)

The microscopic identification of pus cells in the urine is of primary importance because too often laboratory technicians report as pus epithelial cells and other debris in the urine. Unless the cell shows the characteristic trilobate polymorphic "pawnbroker's" nucleus, it is not a pus cell. The addition of a drop of methylene blue 1 per cent acetic acid to the microscopic preparation will accent the polymorphic nucleus.

Five to eight leukocytes per low power field in the uncentrifuged fresh specimen may be considered abnormal. In examination of the urine we use the centrifuge only to throw down bacteria for gram-stain identification or for the acid-fast stain for tubercle bacilli. The amount of pus present does not necessarily reflect the severity of the urologic disease, for even in advanced obstructive uropathy, in the absence of infection, pus cells may be few or absent. Clumping of pus cells merely suggests that a large number are present. In some of our cases of far advanced uninfected hydronephrosis in children, the initial diagnosis based on routine urinalysis had been chronic interstitial nephritis.

In urinary infection the dominant lesion must always be considered to be in the renal parenchyma until proved otherwise. The clinically convenient designation of pyelitis is commonly applied in these cases, but, histologically, interstitial suppurative nephritis is the usual finding, the infection and inflammation of the renal pelvis being relatively mild and of negligible clinical concern. In short, in these cases the bulk of the pus present in the urine originates in the innumerable perivascular inflammatory processes in the interstitial variably suppurative lesions between the tubules of the renal parenchyma.

Acute Urinary Infection. Today this appears to be of somewhat lesser incidence than formerly. These infections are generally self-limited and clinically disappear in seven to ten days irrespective of treatment. But the patient must not be considered cured until at least two sterile cultures of catheterized or otherwise properly collected specimens of urine have been obtained. With failure to observe this dictum the infection will be found still present six months later in half of the patients. With intercurrent infection elsewhere or with debility there is generally periodic exacerbation of the asymptomatic smoldering process and the clinical recurrence of "acute pyelitis."

The history in many of these children discloses several attacks of recurrent "pyelitis." The likelihood of prompt bacterial cure is far greater today with the administration of our modern chemotherapy and newer antibiotics according to bacteriologic indication.

Unfortunately not all infants and children with acute urinary infection progress to smooth convalescence; some remain extremely sick, and the temperature stays high. The diagnosis of persistent acute pyelitis is then commonly made. When the child with acute urinary infection fails to respond to intensive chemotherapy, antibiotic therapy or both

within three days, complete urologic examination should be carried out promptly. A congenital obstruction at the ureteropelvic junction with acute infected hydronephrosis is the most frequent finding. Often the kidney is riddled with minute, yellowish suppurative foci. A renal carbuncle sometimes exists, and there may even be secondary perinephric abscesses; rarely the lesion is acute renal infarction or thrombosis. Yet it may be simply a severe increase or intensification of the existing acute infection. At any rate, the condition is almost always a surgical one which demands prompt recognition and intervention if the child's life is to be saved. Conservative surgery with the liberation of pus by incision and drainage or the establishment of free urinary drainage by catheter will often suffice, although nephrectomy may be necessary. In some of our cases of acute infected hydronephrosis revealed by investigation in turn demanded by persistence of "acute pyelitis," the maintenance of free drainage of the infected renal sac by indwelling ureteral catheter has resulted in prompt general improvement and control of the infection. At a later date the plastic or other surgical procedure necessary can be carried out and with much less risk and far greater likelihood of success than at the height of the acute infection.

Chronic Urinary Infection. This is commonly and inadequately diagnosed as chronic pyelitis and is the most frequent indication for urologic examination in the young. Complete urologic examination should be carried out in any child when intensive chemotherapy for two to three weeks fails to eradicate the infection. Even should the patient be cured, as evidenced by two negative cultures of properly collected specimens of urine, he should not be discharged until at least a satisfactory excretory urographic study has been carried out to prove the absence of obstruction or other lesions which a priori predispose to the initial incidence of urinary infection or may intensify an existing one. Failure to demonstrate a morphologically and functionally normal urinary tract anticipates the recurrence of infection. In the absence of infection the renal damage engendered by unrecognized urinary stasis and back pressure continues, the clinical picture of chronic interstitial nephritis commonly appears later, and sometimes the kidney injury is ultimately fatal. Meanwhile hypertension or growth retardation may be noted. In short, the preventable and remediable obstruction or infection which initially caused the damage still remains unrecognized for want of adequate urologic investigation. These tragedies are the fruits of medical neglect.

Our own diagnostic investigations of infants and children with persistent pyuria have demonstrated practically every lesion of the urinary tract known to exist in adults except cancer of the penis and prostate. The more important lesions are predominantly congenital and obstructive, causing urinary stasis, which not only predisposes to infection, but also perpetuates one already established. Of the lesions schemati-

cally shown in Figure 1, the commonest are congenital strictures of the ureter and urethra. The ureteral narrowings in order of their frequency occur at the ureterovesical junction, ureteropelvic junction and in the body of the channel. Other frequently encountered congenital obstructions include vascular blockage of the renal pelvic outlet, ureterocele, congenital obstruction at the vesical outlet or in the deep urethra (contracture of the vesical outlet, spastic neuromuscular disease of the vesical neck, hypertrophy of the verumontanum, congenital valvular obstruction of the prostatic urethra), congenital urethral stricture and, particularly, congenital stenosis of the external urethral meatus. Complicating (1) vesical diverticula due to urinary back pressure, or (2) urinary calculus, the formation of which is encouraged by urinary stasis or infection, occurs in 3 to 5 per cent of these cases of congenital lower tract obstruction.

About one in 50 young patients with "chronic pyelitis" has caseous renal surgical tuberculosis which, when unilateral, demands nephrectomy.

The treatment of chronic urinary infection will be predicated on the diagnostic findings. In some cases it may be conservative by periodic progressive instrumental dilatation and in others radical by major surgery. Unfortunately nephrectomy is demanded in a great many infants and children with chronic pyuria, although today renal conservation by ureteropelvioplasty is being more widely practised. Having corrected the anatomic lesion and established free urinary drainage, we should not discharge the patient as cured until sterilization of the urine has been achieved.

Disturbances of Urination

The most common of these are dysuria, frequency, urgency, or strangury, and generally reflect acute inflammation due to infection, although congenital obstruction of the lower urinary tract usually exists as the fundamental condition. Sometimes the urinary dysfunction results from congenital neuromuscular vesical disease, in turn consequent to faulty lumbosacral vertebral closure and collateral neural maldevelopment. Yet the vesical disturbance may result from bladder stone or, as we have several times found, a foreign body such as a hairpin or bobby pin which the child introduced into his bladder as a masturbatory act. Adequate urologic examination may be expected to disclose the cause of the bladder disturbance and will be the guide to rational therapy.

Hematuria

In order of their etiologic relationship, hematuria in the young is most commonly caused by acute urinary infection, acute nephritis,

ulceration of a stenosed external urethral meatus or tumor of the urinary tract. The most common causes of blood in the urine are schematically indicated in Figure 2. Except when conclusively due to acute nephritis, hematuria demands a prompt, complete urologic examination, preferably while the bleeding is taking place.

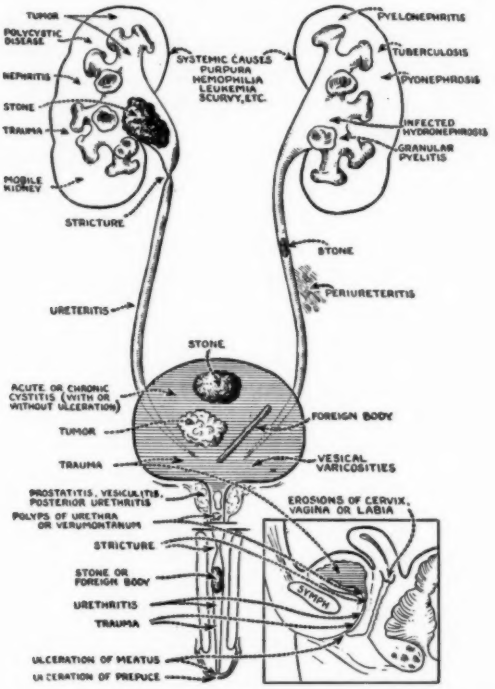

Fig. 2. Usual causes of hematuria. Additional systemic, allergic, toxic and other unusual causes of hematuria are enumerated in the text. (Campbell: Clinical Pediatric Urology.)

Hematuria caused by infection alone usually responds to intensive chemotherapy and antibiotic therapy. Unsuspected obstruction, stone or tumor may be disclosed by the examination, and requires appropriate treatment. Hematuria is relatively common with hydronephrosis and other lesions resulting from urinary back pressure and reflects the congestion of the urinary passages above the point of obstruction. On the other hand, hematuria is one of the less common symptoms of renal embryoma or Wilms' tumor of the kidney, and appears late, only after ulceration of the growth into the pelvis has occurred.

Abdominal Pain

As suggested in Table 1 and in Figure 1, abdominal pain may result from a wide variety of urologic lesions, the majority of which are of the obstructive variety and include ureteral kink, stone or blood clot, blockage at the bladder outlet, urethral stricture or a stenosed external urethral meatus. Attention cannot be too forcibly directed to the fact that patients of all ages with persistent abdominal pain due to urologic lesions commonly have associated gastrointestinal disturbances which

TABLE 1. *Chief Potential Causes of Abdominal Pain of Urologic Origin*

LOCATION	CAUSE
Kidney	Abnormal mobility, ectopia, horseshoe formation, fused, hydronephrosis, calculus, tumor, pyelonephritis, pyonephrosis, solitary abscess, perirenal tumor, cysts or abscess
Ureter	Obstruction by stricture, stone, kink, diverticulum, compression by (*a*) aberrant vessel, (*b*) fibrous bands, (*c*) periureteral masses
Bladder	Stone, retention (neuromuscular, contracted outlet, prostatic obstruction), tumor
Urethra	Stricture, meatal stenosis, stone, valves, hypertrophied verumontanum, diverticulum
Adrenal	Tumor or abscess
	Infection or inflammation of these structures

receive the chief therapeutic attention. Meanwhile, the underlying etiologic uropathy remains unrecognized.

Gastrointestinal disturbance often accompanied by abdominal pain is the outstanding manifestation in over half of the children with chronic urinary obstruction or infection. There may be diminished or total lack of appetite, indigestion, flatulence, constipation, anemia, malaise and growth retardation; in older patients the diagnosis of gastric or duodenal ulcer, gallbladder disease or chronic appendicitis is too often erroneously made. When the urologic disease as identified by adequate examination is corrected, not only will the abdominal pain and digestive upsets disappear, but the child's appetite will return and he will rapidly gain in strength, weight and appearance.

Abdominal Tumors

Hydronephrosis is the commonest abdominal tumor in the young, while Wilms' tumor and adrenal neuroblastoma rate second and third respectively in incidence. In almost every instance in a child the hydronephrosis is of congenital etiology and may be well developed at birth

or be noted in early infancy. In most cases of palpable hydronephrosis in this age group the obstruction is at the ureteropelvic junction, most often a congenital stricture, but occasionally caused by aberrant lower polar renal vessels which traverse and compress the ureter. A suprapubic tumor in a child is most likely to be distended bladder, although the possibility of renal ectopia, hydrometrocolpos, ovarian cyst or anterior sacral dermoid must not be overlooked. *Any solid abdominal tumor in a child should be considered malignant until proved otherwise.* When the tumor is neoplastic, the earlier it is recognized and excised, the better the prognosis. In most instances urologic investigation is necessary to establish the anatomic diagnosis; here retrograde pyelography, preferably bilateral, is diagnostically definitive.

Anomalies of the External Genitalia

In a third of the cases of external genital malformation the upper urinary tract is also anomalous. In my experience, in males ureteral reduplication has been the most frequently observed upper tract anomaly, although ureteral stricture, ureterocele or malformations at the bladder neck or in the deep urethra are sometimes found. In the female with double uterus and with or without double vagina, congenital unilateral renal agenesis or hypoplasia has been of serious clinical concern in several cases.

Because of this high correlation of anomalous development, we routinely perform excretory urography as part of the study of these patients, and even in simple balanitic hypospadias. Cystoscopic examination is not always carried out in hypospadias except in the more advanced cases, in many of which a greatly dilated utricle exists. The development of hypospadias in the male reflects undue estrogenic hormonal influence in early fetal life, and the gradation of feminization is reflected in the persistence of the dilated termination of the müllerian ducts in the verumontanum. In several of the more pronounced cases of hypospadias, and particularly in the pseudohermaphroditic variety, we have found an abbreviated uterine formation even with one or two fallopian tubelike extensions into the pelvis. Excretory urography carried out in a three year old boy with a simple balanitic hypospadias and congenital stenosed external urethral meatus disclosed an unsuspected asymptomatic tight congenital stricture of the lower third of the right ureter with pronounced ureteral dilatation and mild hydronephrosis above.

Urogenital Injury

Injury of the urinary tract calls for at least a satisfactory excretory urographic study to ascertain whether urinary or hemorrhagic extravasa-

tion exists. The lacerated urethra or bladder may be outlined by urethrography or cystography, the extent of rupture and extravasation being demonstrated. In renal injury the excretory study should be made before the onset of shock; otherwise there may be inadequate or no renal excretion. The degree of renal injury is reflected in diminished renal function. When the excretory urographic examination is unsatisfactory or the condition of the patient is grave or if there is continued profuse hematuria, complete instrumental examination should be performed without delay in order that proper surgical treatment may be instituted in time to save life. In injuries of the urethra such as follow straddle injury (rupture), for example, the establishment of free bladder drainage by indwelling catheter will usually forestall urinary extravasation and periurethral phlegmon.

Injury and Disease of the Spinal Cord

In acute trauma of the nervous system, and especially of the spinal cord, urologic investigation should be instituted promptly, but not until the condition of the patient has improved sufficiently to warrant completion of the anatomic diagnostic survey. In this interim free bladder drainage must be maintained by cystostomy, indwelling catheterization or trocar cystostomy.

Most spinal cord injuries in the young result from traffic accidents and falls and are comparatively rare. Immediately after the acute spinal cord trauma sphincterospastic vesical retention with overflow appears and demands prompt drainage; here suprapubic drainage by trocar cystotomy is favored over continuous indwelling catheterization. Urinary control returns in varying degrees in most of these patients; when reliable vesical control and emptying are satisfactorily re-established, the tube is discontinued. In some instances vesical evacuation is later achieved by limited transurethral resection of the vesical outlet. Accurate urologic and topical neurologic diagnosis is the guide to rational treatment, which in these cases is commonly unsatisfactory.

Most neuromuscular disease of the urinary tract in the young results from lumbosacral malformation of the vertebral column and spinal cord. With this anomaly large segments of lumbosacral innervation are frequently congenitally absent—they simply fail to form or, having formed, the nerve structure subsequently degenerated (spina bifida, meningocele, myelocele, meningomyelocele).

Occasionally the vesical dysfunction is secondary to nervous system infections, inflammations or degenerative changes as seen in poliomyelitis, transverse myelitis or syringomyelia, for example. Here, too, accurate determination of the nature and extent of the vesical involvement, of the status of the sensorium, and of the motor potential of the

bladder and urinary apparatus is imperative before a relatively precise prognosis can be given or rational therapy instituted.

Enuresis

Unconscious passage of urine occurs predominantly in children and at night, but also is observed in the daytime in about 10 per cent of all enuretics. This extremely frequent condition is a functional manifestation in over 95 per cent of the patients, reflecting maladjustment of the child or his feeling of insecurity, being unwanted or parental neglect. When enuresis persists for three or four months despite intensive medical treatment and psychotherapy (encouragement, gold stars, belladonna or any of 400 drugs given in the past), a complete urologic study should be carried out. Normal bladder control is achieved between the twenty-eighth and thirtieth months of life and often much earlier. We rarely advise or carry out urologic examination of enuretic children under four years of age. Yet, in over 1600 enuretic children personally studied urologically because of therapy resistance, disease of the urinary tract adequate to explain the incontinence was disclosed in nearly two thirds. Approximately one in seven of these children could not empty the bladder completely, but retained residual urine. Sometimes this residuum resulted from neuromuscular disease, but was often due to unsuspected congenital obstruction along the lower urinary tract, notably at the vesical outlet. When organic urologic disease is demonstrated, it should be corrected according to the indications, and in a gratifying number of these patients treated on this basis the establishment of normal urinary continence has been achieved. Equally important, when the urologic investigation discloses no organic disease to explain the incontinence, psychotherapy and medical measures may again be resumed and continued with the knowledge that the urinary tract is suffering no damage.

Renal Insufficiency

This may result from bilateral renal hypoplasia or congenital absence of one kidney with renal hypoplasia of the opposite side. In older children the renal insufficiency may result from severe antecedent disease such as nephritis consequent to severe exanthemata or to pronounced renal infection with widespread kidney destruction, sclerosis and fibrofatty replacement. Another common cause is urinary obstruction, which in the young is generally congenital; the resulting back pressure produces hydronephrotic renal injury, often with far advanced damage and correspondingly reduced renal function. In the study of the patient with chronic nephritis, urologic examination is a great help in the determina-

tion of the renal function and anatomic status, and properly should be a part of the complete investigation.

Retarded Growth

Advanced renal injury by disease or functional deficiency in infancy and early childhood is frequently reflected in growth retardation: the earlier the severe renal disease appears, the greater is the physical retardation. The more frequently observed lesions in delayed growth caused by renal dysfunction are (1) bilateral renal hypoplasia, (2) congenital absence of one kidney with hypoplasia or grave disease of the other, (3) urinary back pressure injury consequent to bilateral ureteral obstruction or, most commonly, (4) congenital blockage at the vesical outlet or in the adjacent prostatic urethra. We have seen it with congenital stenosis of the external meatus.

In these cases complicating infection generally accelerates the renal damage, and it is not unusual to find a ten year old child presenting the stature of four years, yet appearing unduly aged. For this reason all undersized children and those whose growth is slow for unknown reasons should have the benefit of at least a satisfactory excretory urogram to determine whether the urinary tract is anatomically and functionally normal and, if not, what is the nature and extent of the lesions present. In these children the skeletal changes commonly become those of osteitis fibrosa cystica, a condition often designated as renal rickets.

When the urinary tract disease is remediable, and proper therapy based on the urologic findings is carried out, the child usually starts to grow. On the other hand, the longer the renal deficiency disease persists, the greater and more permanent will be the growth handicap.

Hypertension

During recent years studies of the problem of hypertensive vascular disease have attributed the condition to unilateral nephropathy in about 1 per cent of the cases. In most of this group the kidney and its blood supply are congenitally hypoplastic; in short, the pathologic picture resembles that of the experimental Goldblatt kidney. Many more cases, however, show sclerotic chronic pyelonephritis, which, in turn, is generally the late result of long-standing "chronic pyelitis" dating from early childhood. In unilateral renal disease with associated hypertension, nephrectomy has often been followed by fall of blood pressure to more normal levels. The results should not be considered a cure unless the diastolic pressure in particular remains within normal range for at least two years. Moreover, nephrectomy should not be performed as a cure of hypertension except, possibly, in pronounced unilateral renal hypo-

plasia; i.e., the kidney should be removed solely because it is diseased and would be excised were there no hypertension.

SUMMARY

The indications for urologic examination in children are essentially the same as in adults. The indications for such an examination should be recognized early so that the sick child may have prompt treatment and the best chance for permanent cure rather than be subjected to the risk of a life of invalidism or, even more grave, suffer early death. The proper collection of the urine specimen for analysis and bacteriologic study is a most important consideration in the investigation. It is now possible to carry out complete cystoscopic examination with bilateral retrograde pyelographic studies even in newborn males, the technical details of the investigation being the same in patients of all ages.

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URINALYSIS IN PEDIATRIC PRACTICE

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Urinalysis is the keystone of pediatric urology, for simple tests on the urine will often obviate more complicated procedures or will direct one immediately to definitive investigation. A careful examination of the urine is one of the most important procedures done in pediatric practice, but unfortunately it is commonly done in a slipshod manner leading to false conclusions. It is the purpose of this clinic to point out the techniques of urinalysis that will allow one dealing with children to interpret the findings correctly.

METHODS OF COLLECTION OF URINE

Single Specimens

For routine purposes casually voided specimens in the office are more satisfactory than specimens collected at home, for the urine should always be *fresh* when examined in order to avoid bacterial growth, alkalinization of the urine and the resulting destruction of any formed elements present. However, a first morning specimen collected at home may be desired, since it usually shows maximal concentration, or it may be easier to obtain a voided specimen from an infant at home. In these instances the urine should be kept refrigerated until brought to the office. In hospital practice first morning specimens should be collected, but there must be a minimum of delay after collection until the examination is made. Mothers must be instructed to be sure that a girl's genital area is clean before voiding, for one of the most important errors is due to contamination of the urine with pus cells from the vagina. Contamination of a small boy's urethra with pus cells is not a problem if the meatus is not covered by the foreskin.

Urine may be collected from infants who will not void on demand by

various devices. Among the simpler are instructing the mother to have a basin at hand to catch voluntary voiding during feeding or bath time, having the undiapered baby nap on a rubber or plastic sheet, or having the mother put a pad of cotton in an infant's waterproof pants and then squeezing the urine out. In hospital practice strapping a large test tube to the penis (Fig. 3) or a birdseed container to the cleansed vulva (Fig. 4) is effective. Placing loose cotton in the birdseed container makes the collection more satisfactory and does not strain out the cells. *No such devices are satisfactory for urine cultures* regardless of how well the skin is cleansed.

Complete Specimens

In order to collect 12 or 24 hour specimens, male infants may be prepared (Fig. 5) by attaching a finger cot to the penis with a medicine

Fig. 3. Fig. 4.

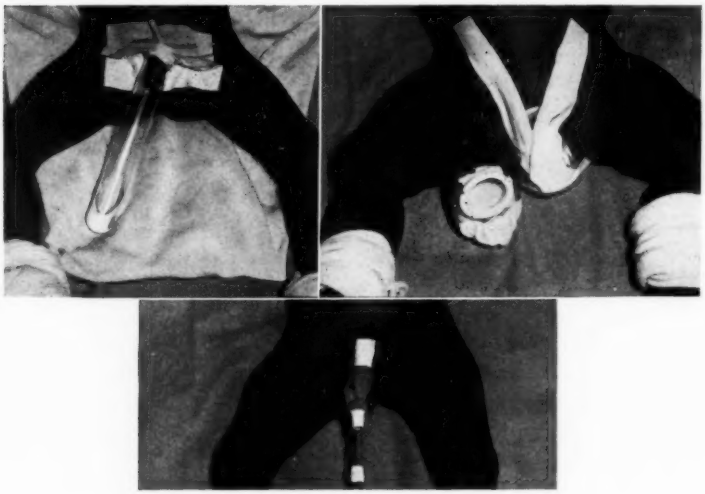

Fig. 5.

Fig. 3. Test tube collection of urine from male infant.
Fig. 4. Birdseed container for female infant.
Fig. 5. Continuous "external catheter" collection.

dropper fastened to the other end connecting to a suitable container. Techniques for girls are less satisfactory, but can usually be accomplished by using a "metabolism" bed having a hole cut in the center of the mattress, over which the child is restrained.

Specimens for Bacteriologic Study

Whenever pus or bacteria are found in voided specimens, confirmation and bacterial identification must be sought by "clean catch" or catheterized specimens. In cooperative older children "clean catch" specimens are better than catheterized specimens for bacteriologic study *if properly obtained.* In the boy this is done by careful washing of the prepuce with soap, followed by Zephiran or 1:1000 bichloride of mercury. The child then starts to void, and one catches the midpoint of voiding by introducing a sterile vessel into the urinary stream. *Voiding must have started before "catching" the specimen in order to wash out the anterior urethra.* Getting "clean catch" specimens in girls is more difficult, but it can be done in older children if the labia are held apart, the vulva is cleaned, and a specimen caught from the unimpeded urinary stream.

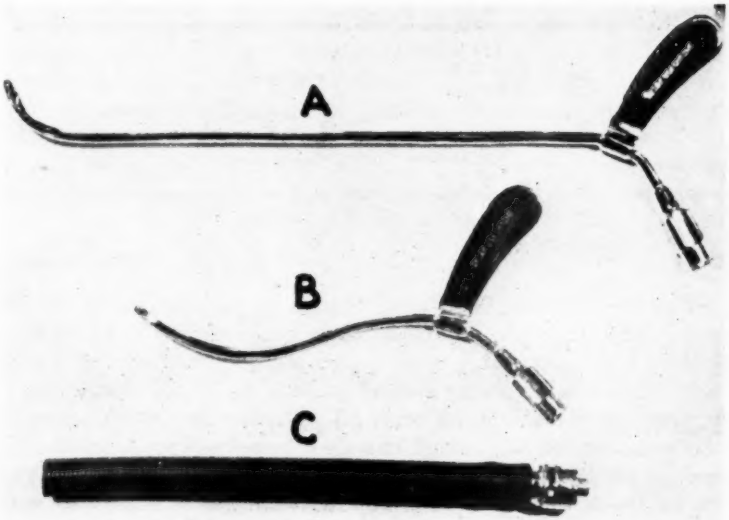

Fig. 6. Campbell's miniature (8 F.) metal catheters. A, Male catheter. B, Female catheter with generous fin handle and female Luer connecting tip. C, Rubber tubing with male Luer connection fitting to facilitate collection of catheter specimen or irrigation of the bladder. (Courtesy of Journal of Urology.)

Catheterization of boys is done in the usual way with number 8 to 12 rubber catheters. Short metal catheters (Fig. 6) are useful for girls. A rubber tip on the end allows one to control the flow of urine into the sterile container.

PHYSICAL CHARACTERISTICS

Amount

The commonly accepted volumes of urine voided in 24 hours are listed in Table 2. Approximately one third of newly born infants may not void for the first 24 hours.

TABLE 2. *Average Daily Output of Urine*[1]

AGE OF CHILD	OUTPUT (MILLILITERS)
1–2 days	15–60
3–10 days	100–300
10 days–2 months	250–450
2 months–1 year	400–500
1–3 years	500–600
3–5 years	600–700
5–8 years	650–1000
8–14 years	800–1400

Color

Various drugs and foods cause changes in the color of an infant's urine, but the most confusing is the redness looking like blood occasionally seen after eating beets. In general an infant's urine is fairly pale unless associated with marked dehydration, biliary obstruction, or hemoglobin or blood in the urine. All red urines should be checked by the benzidine test for hemoglobin, since hemolysis may have occurred and no intact red cells may be present. A simple and satisfactory test for biliary obstruction is to shake a test tube partly filled with urine and observe the yellow foam due to the presence of bile pigments.

Specific Gravity

No test is more easily done, nor so often neglected, than measuring the specific gravity of the urine. Physicians are all too prone to order complicated and expensive tests of kidney function when observation of the specific gravity would give the information required. The urine may vary from 1.001 to 1.030 in health, but in the presence of nephritis both concentration and dilution may be so impaired that the specific gravity fixes at 1.008 to 1.010. In general, the ability to concentrate the urine is the more important phase and can be tested by obtaining single early morning specimens or by the Fishberg test. In this test no fluids are given after supper. A specimen is obtained on awakening, again one hour later, and again, if desired, after being up one hour. Except in early infancy, failure to concentrate the urine above 1.010 indicates kidney damage, but the ability to concentrate the urine to above 1.022

indicates good enough function so that other function tests are unnecessary. *Excretory urograms will not be satisfactory if the child cannot concentrate to specific gravity above 1.015.*

Reaction

Most urines have a reaction of approximately *p*H 6.0, but alkaline urines may be obtained after a large intake of citrus fruits. Otherwise an alkaline urine should make one suspicious that the urine has been standing for some time and has become alkaline by the conversion of urea to ammonia. It is particularly important to relate the *p*H of the urine to the patient's electrolyte balance, for it will often allow one to make the important distinction between such conditions as metabolic acidosis, in which a low plasma carbon dioxide content is found, but an acid urine, and respiratory alkalosis, in which the blood carbon dioxide content may also be low, but the urine is alkaline.

CHEMICAL TESTS

Albumin

The most commonly used methods of measuring the amount of albumin in the urine are the heat and acetic acid test and the sulfosalicylic acid test. The former is done by boiling approximately 5 ml. of urine in a test tube and then adding a few drops of acetic acid. The addition of acetic acid is primarily to dissolve any alkaline crystals present, but in some instances it precipitates small amounts of protein otherwise not detected. The latter test is done by adding approximately 1 ml. of 3 per cent sulfosalicylic acid to 1 ml. of urine or, for more quantitative results, adding 7.5 ml. of 3 per cent sulfosalicylic acid to 2.5 ml. of urine in special Kingsbury-Clarke tubes and comparing them with a gelatin-formazine standard. Table 3 shows the commonly accepted comparison of these qualitative and quantitative tests. A normal

TABLE 3. *Comparison of Quantitative Tests for Albumin in the Urine with Rough Qualitative Descriptions*

QUALITATIVE	DESCRIPTION	QUANTITATIVE (mg./100 ml.)
−	Negative	0
±	Very slight trace	0–10
+	Slight trace	10–50
++	Moderate cloud	50–200
+++	Heavy cloud	200–500
++++	Very heavy cloud*	More than 500

* Urine "boils solid" at 3.0 gm./100 ml.

child may show from 0 to 15 mg. per 100 ml. of urine. A child with nephritis may run from 20 to 600 mg. per 100 ml., and a child with nephrosis may excrete as much as 500 to 3000 mg. per 100 ml. Slight albuminuria (under 50 mg. per 100 ml.) is not uncommon in children without renal disease, being caused by fever, exercise or heavy protein meals. Persistent albuminuria must be investigated and occasionally may disappear on lying down, the so-called orthostatic albuminuria.

Sugar

The presence of reducing substances in the urine as shown by the usual tests with Benedict's solution usually is associated with abnormal amounts of glucose, but one must be alert to carry out further tests when indicated in order to recognize the occasional case of galactosuria or pentosuria. Falsely positive tests may be associated with fright, the concurrent administration of intravenous glucose, or administration of large amounts of thiamine or ascorbic acid.

Ketone Bodies

Infants are particularly susceptible to ketosis due to starvation in association with gastrointestinal disease, so that tests for acetone and di-acetic acid should be done routinely on urines from sick children. It is particularly important to have this information when one is assessing a child's electrolytic balance.

MICROSCOPIC OBSERVATION

For most purposes an uncentrifuged, *fresh* urine specimen is more valuable than a centrifuged specimen except for bacteriologic smears. This is because the concentration of a few cells may give a false diagnosis of pyuria or hematuria. One does not usually consider it abnormal to find as many as six to eight white blood cells per low power microscopic field in an uncentrifuged voided specimen from a girl or as many as two or three white blood cells per low power field in a voided specimen from a boy or a catheterized or "clean catch" specimen from a girl. An occasional red blood cell per low power field is also normal. Centrifuged urine specimens are of value in following up renal disease such as by the Addis count, but one must not accept the diagnosis of pyuria solely on the finding of pus cells in a centrifuged urine. It is also most important to distinguish epithelial cells with their large, single nucleus from pus cells to avoid a similar false diagnosis. The presence or absence of clumping of white blood cells is probably not of much significance.

TABLE 4. *Maximal Values for a 12 Hour Addis Count in Children*[2]

CONSTITUENTS	NUMBER
Red blood cells	1,000,000
Epithelial and white blood cells	1,000,000*
Casts	10,000
Protein	40 mg.

* Uncatheterized urines from girls may show as many as 2,000,000 epithelial and white blood cells.

Addis counts must also be interpreted with caution unless done carefully by trained personnel. Although there is some variation in standards of normal, Table 4 gives a generally accepted range of findings.

BACTERIOLOGIC EXAMINATION

Smears

It must be stressed again that specimens must be obtained without contamination by "clean catch" or catheterization to be of any value for bacteriologic examination. The fresh urine should be centrifuged for five minutes at 2500 revolutions per minute and the sediment smeared for staining. A stained smear is of definite value in establishing an early diagnosis of bacteriuria and in identifying the organisms as gram-positive or gram-negative. The significance of only an occasional organism on smear may not be great, but must be confirmed by *quantitative* bacteriologic means. Gram staining should be routinely done in specimens showing pyuria. When tuberculosis is suspected, either acid-fast or the fluorescent dye, auramine O, techniques must be used for identification.

Culture

Routinely urine specimens should be plated on blood agar plates, using 0.5 ml. of urine spread over the plate, as well as inoculated into beef infusion and glycolate broths (the last to identify anaerobic organisms). The quantitative results obtained from the plate technique help the clinician assess the significance of a positive culture. The growth of aerobic organisms in the broth but not in the plates indicates probable contamination during collection rather than actual bacteriuria. Reports from laboratories of positive cultures without other quantitative information are usually more misleading than not.

Sensitivity tests are of definite although limited usefulness. They should be run on all organisms obtained from the urine to serve as a base line for later observations or to help in picking the right chemotherapeutic agent in resistant or recurrent infections.

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UPPER URINARY TRACT ANOMALIES

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Many anomalies, that is, developmental defects, of the upper urinary tract are compatible with a normal life span and are not in themselves productive of symptoms. Most, however, particularly if an obstructive component be present, predispose to pathologic changes, usually those associated with back pressure and infection. In our approach to the clinical management of anomalies of the kidney and ureter we must then bear in mind the following points:

1. When an anomaly is demonstrated urographically, we must determine whether it is actually of clinical significance itself or whether it is a mere incidental finding of no importance.

2. In cases of recurrent, persistent or severe urinary tract infection in infants and children one must suspect an anomaly as the underlying cause.

3. Likewise, in the pediatric problems of obscure abdominal pain, gastrointestinal disturbances, growth retardation and unexplained fever, the likelihood of an upper tract anomaly is considerable, even though the urinalysis be negative.

4. Detection of an anomaly early in life by adequate urologic study often permits correction of the lesion before *irreparable* kidney damage has taken place. To be sure, not every anomaly is remediable, but even here an adequate work-up permits an intelligent prognosis. In short, the importance of an early and complete urologic study is indispensable in the successful management of upper tract anomalies.

The explanation of upper tract anomalies is found in the arrested or faulty embryologic development of the parts. It will be remembered that the kidney has a dual origin. The ureteric bud arises as an outgrowth from the wolffian duct just outside the entrance of the latter

into the primitive cloaca. As this bud grows, it becomes capped by a mass of mesodermal tissue called the "metanephric blastema." The upper end of the bud divides and gives off successive branches which in time come to represent the collecting system of the permanent kidney, namely, the ureter, pelvis, major and minor calyces, and collecting tubules. The metanephric blastema or nephrogenic cap differentiates to form the secretory and resorptive elements of the kidney, namely, the glomeruli, proximal convoluted tubules, loops of Henle, and distal convoluted tubules, which in turn proceed to join with the collecting tubules and more distal excretory passageways. In the further differentiation of the cloaca and wolffian duct to form the definitive bladder and genital ducts, the lower end of the ureter comes to terminate within the definitive bladder. In early embryonic life the kidney lies within the pelvis, but soon ascends and rotates to assume its final position in the lumbar fossa with its pelvis lying medially and the calyces pointing laterally. Various anomalies occur when this normal mechanism goes awry.

RENAL ANOMALIES

A classification of anomalies is given in Table 5. From this list I have chosen for individual discussion those which, because of their

TABLE 5. *Congenital Anomalies of Kidney**

I. OF NUMBER
- A. Bilateral agenesis
- B. Unilateral agenesis (solitary kidney)
- C. Supernumerary kidney

II. OF SIZE AND STRUCTURE
- A. Hypoplasia
- B. Congenital hypertrophy
- C. Renal cysts
  1. Simple
  2. Multicystic
  3. Polycystic

III. OF FORM (RENAL FUSION)
- A. Horseshoe kidney
- B. Disk kidney
- C. Sigmoid or L-shaped kidney

IV. OF POSITION
- A. Simple ectopia—"pelvic kidney"
  1. Unilateral
  2. Bilateral
- B. Crossed ectopia with or without fusion
- C. Movable kidney

V. OF ROTATION

VI. OF PELVIS
- A. Double kidney
  1. Unilateral or bilateral
  2. Partial or complete
- B. Congenital hydronephrosis

VII. OF VESSELS
- A. Arterial
- B. Venous

* Modified from Campbell.[1]

frequency or importance, merit the practitioner's interest. An awareness of the clinical picture and principles of treatment of these will be most rewarding.

Congenital Solitary Kidney ("Unilateral Renal Agenesis")

Failure of the ureteric bud or of the metanephric blastema to develop on one side accounts for the occurrence of congenital solitary kidney. Reports on the incidence of this anomaly vary from one in 1600 to one in 200. In my own experience it occurs approximately once in every 500 urologic patients. There are no symptoms per se, but statistically the solitary kidney itself is more prone to disease. A presumptive diagnosis is made when on the excretory urogram no function and no kidney shadow on one side are associated with a hypertrophic kidney on the opposite side. Confirmation is obtained by cystoscopy, in which the absence of the ureteral orifice on the side of nonfunction is found. Yet in approximately a third of the cases the ureter is present, but ends blindly.

After the structural and functional integrity of the kidney has been ascertained nothing further beyond reassurance and caution regarding any potential trauma is in order. Annual follow-up intravenous pyelograms for a few years are recommended. As to athletic activity, avoidance of "body contact" sports, such as football, wrestling and boxing, is recommended.

On the other hand, when the solitary kidney itself is abnormal, aggressive efforts, including careful surgery if indicated, are made to clear up infection, promote drainage and conserve all functioning tissue.

Renal Hypoplasia

Faulty development of the renal blastema or perhaps inadequate vascularization occasionally results in a kidney which is structurally much smaller than normal and functionally inferior. Fortunately the lesion is usually unilateral. The hypoplastic organ may or may not be asymptomatic, but is usually characterized by chronic or recurrent infection. Diagnosis is made by urography and functional studies. The condition is difficult to differentiate from unilateral atrophic pyelonephritis, yet this point is really not too important in that in the absence of symptoms no treatment is necessary, whereas if the degree of infection warrants, nephrectomy is indicated in either case.

Most of the proved cases of hypertension of renal origin have occurred in patients with hypoplastic kidney. For this reason the occurrence of hypertension in the young is an indication for complete urologic study; if a hypoplastic kidney is found, its removal is warranted.

Polycystic Kidney Disease

Polycystic kidney disease is a hereditary, congenital defect which may be divided into infantile and adult types. From the etiologic viewpoint,

congenital polycystic kidney disease is felt to result from failure of the secretory elements of the kidney to fuse with the collecting elements. This theory is not universally accepted, but it has the virtue of simplicity.

Characteristically the disease is bilateral and is revealed by abdominal masses representing the enlarged kidneys. In the infantile type early death from renal failure is the rule. At autopsy the kidneys are sponge-

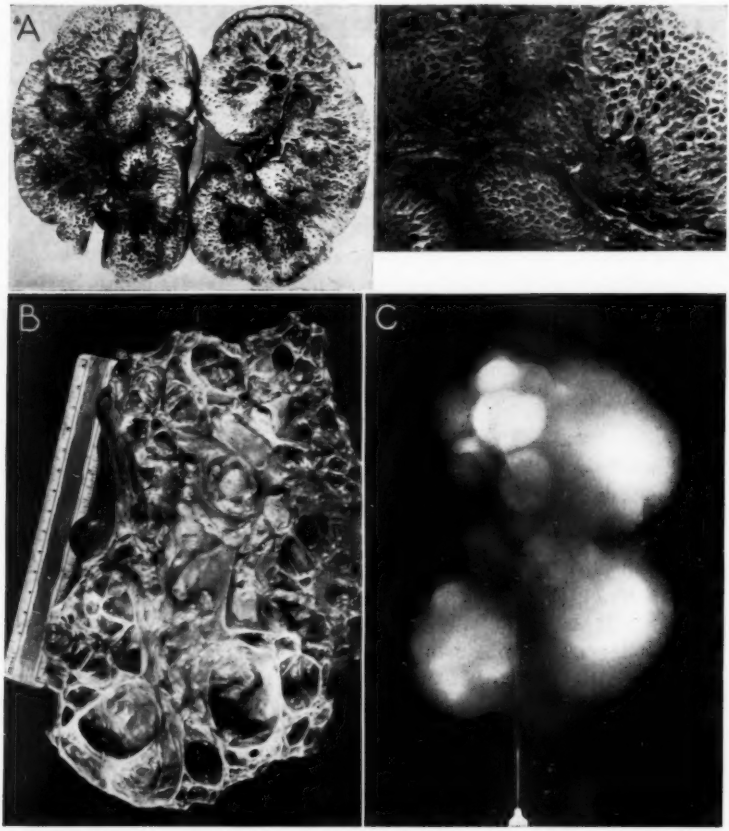

Fig. 7. Types of polycystic kidneys. *A*, Infantile form with spongelike appearance. *B*, Adult form of polycystic kidney disease showing variation in size of cysts. Both the infantile and adult forms of true polycystic kidney disease are typically bilateral. *C*, Radiograph of surgical specimen of "congenital unilateral multicystic kidney"; this is probably a different disease entity from the preceding types and, while congenital, is not hereditary. Because of the difference in prognosis it is well to differentiate between these different types of polycystic disorders. (*A*, reproduced from Anderson's Pathology. 2d edition. St. Louis, C. V. Mosby Co., courtesy of Dr. Anderson and the publishers.)

like structures, the entire renal parenchyma being replaced by innumerable cysts of fairly uniform size (Fig. 7, A). There is no treatment for the condition in infancy, and the prognosis is inevitably poor. On the other hand, if the disease does not become manifest in early life, several decades may pass by before progressive enlargement of the kidneys or symptoms of renal insufficiency bring the patient to the physician. Both medical and surgical measures are sometimes helpful in these late cases, but since they are not primarily a pediatric problem, further consideration is not in order here.

Congenital Unilateral Multicystic Kidney

This entity, though having some of the features of polycystic disease, should in my opinion be regarded as a separate disorder. The reason for this is that multicystic kidney as opposed to polycystic kidney disease is characteristically unilateral and hence does not carry the same dire prognosis. Furthermore, the appearance of the gross lesion is entirely unlike that of the infantile type of true polycystic kidney (Fig. 7, C). In the multicystic form we find marked variation of the size of the cysts, which range in number from a few to a dozen or so, in contradistinction to the infantile polycystic kidney, wherein myriads of uniform cysts replace the kidneys. It is felt that many of the cases of unilateral polycystic kidney reported in the literature actually represent the multicystic form in that the illustrations accompanying them are characteristic of the latter type. Diagnosis usually is made by finding a large unilateral abdominal mass combined with nonfunction on the involved side and a normal contralateral kidney on pyelography. Often the ureter does not communicate with the calyceal system. The differential diagnosis includes hydronephrosis and Wilms' tumor. The treatment of multicystic disease is nephrectomy after the other side has been demonstrated to be normal. The prognosis is good.

Anomalies of Form and Fusion

Horseshoe Kidney. In place of the normal development of two discrete kidneys, the primitive kidney anlagen may fuse. Depending on the type of fusion, we may find an S-shaped, L-shaped, disk-shaped or the familiar "horseshoe kidney," in which the lower poles of the kidneys are joined by a parenchymal isthmus (Fig. 8). This condition may remain asymptomatic throughout life, or its presence may be heralded by the finding of an abdominal mass, urinary tract infection or abdominal pain. The cases I have seen in children have usually been detected by an alert pediatrician finding a midline abdominal mass about the level of the umbilicus. The pyelographic findings are characteristic and

consist in visualization of the horseshoe-shaped outline combined with the calyces pointing medialward rather than laterally and the long axis of the kidney "toeing in."

In the usual form of horseshoe kidney the ureters pass anterior to the isthmus, thereby often causing stasis and hydronephrotic dilatation, with pyelonephritis a common accompaniment.

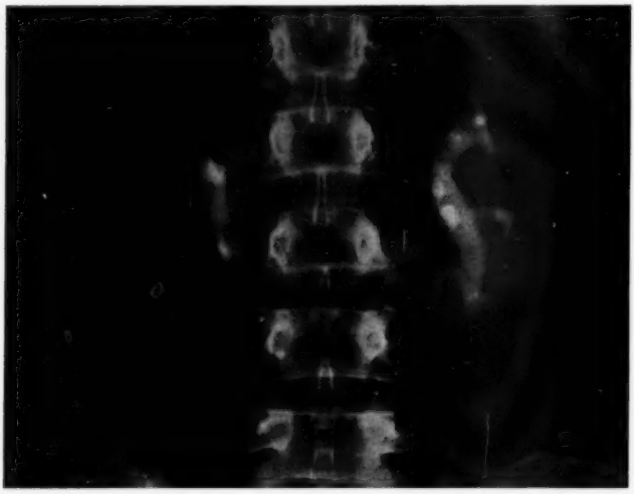

Fig. 8. Intravenous pyelogram of horseshoe kidney. Note isthmus connecting lower poles of the two halves and medial deviation of several calyces.

In the absence of urinary tract infection and obstruction, no treatment is indicated. Should the presence and severity of these factors warrant it, however, then operation may be necessary. This consists in cutting the bridge of tissue joining the kidneys and restoring the normal axis so that drainage of the pelves is unimpeded. Any associated action such as removal of stones, straightening of kinks, and the like, is of course carried out. Occasionally removal of a hopelessly diseased half of the fused organ is necessary. Once a fused kidney is detected, even though at the time no operative measures are necessary, systematic follow-up urograms are in order.

Ectopic Kidney

The kidney may become arrested in its normal ascent on one or both sides so that its permanent position lies within the bony pelvis or in the iliac fossa (Fig. 9). There is an associated malrotation and anomalous

blood supply. Another feature is a short ureter, which differentiates a true ectopic kidney from nephroptosis.

The diagnosis of an abnormality of position is suspected from the excretory urogram and confirmed by retrograde pyelography. A normally functioning ectopic kidney may be overlooked on the excretory urogram because the organ overlies bone, but closer scrutiny may reveal a suggestion of displaced calyces, which are a clue to the situation.

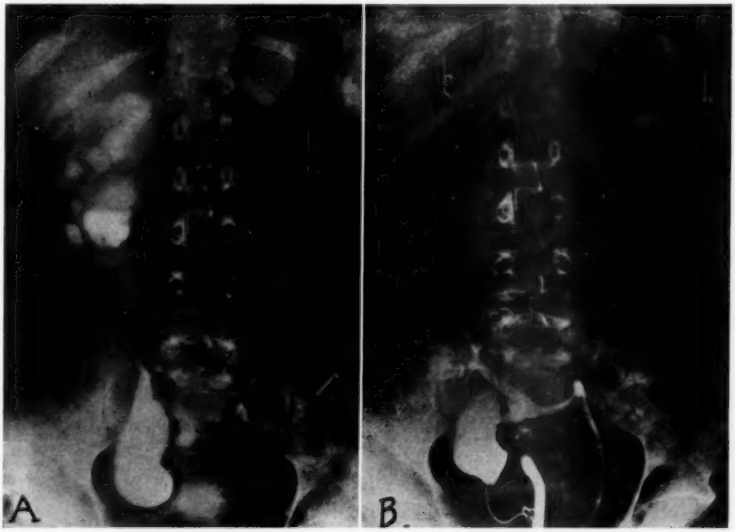

Fig. 9. Combination of anomalies. The left kidney lies within the hollow of the sacrum, but is otherwise reasonably normal; destruction of right kidney (*A*) due to lower ureteral stricture. A "mass" was felt within the pelvis at the time of appendectomy for "chronic appendicitis" with no previous urologic work-up. Subsequently right nephro-ureterectomy was done, and the patient remains in health with normally functioning ectopic kidney (*B*) some 15 years later. (From author's article, courtesy Journal of Urology, Vol. 71, Williams & Wilkins, Baltimore, Md.)

As with the horseshoe kidney, symptoms may be absent and the condition detected on routine physical examination as an abnormal abdominal mass in the iliac fossa or even, in the case of a pelvic kidney, by vaginal or rectal examination. However, the ectopic kidney is particularly prone to stasis and infection as well as being a cause of atypical pain. Not infrequently the condition is first discovered at exploratory laparotomy performed for bizarre abdominal symptoms or "chronic appendicitis" when the patient has not had the benefit of previous urologic investigation. Here, removal of the "mass" is ill-advised.

Most patients with an ectopic kidney require no treatment beyond the clearing of infection, reassurance and observation. Occasionally

pain, resistant infection or destruction of function makes nephrectomy advisable. Conservative surgical measures in the ectopic kidney are rarely successful. The operative removal of an ectopic kidney is technically difficult and should not be embarked upon lightly.

Malrotated Kidney

Bizarre pyelograms sometimes result from failure of the normal rotation of the kidney whereby the organ reaches its proper site, but the pelvis remains anterior. Oblique and lateral exposures clarify the condition, which is usually a coincidental finding and of no clinical significance.

Congenital Hydronephrosis Due to Obstruction at the Ureteropelvic Junction

This is one of the most important anomalies of the upper urinary tract both because of its frequency and because, if the condition is discovered early, the kidney may be saved, whereas, if the lesion is uncorrected, loss of the kidney is inevitable. Furthermore, in a significant percentage of cases the condition is bilateral. From the pathologic viewpoint there are several types of ureteropelvic obstruction, including extrinsic bands, aberrant blood vessels, intrinsic stenosis or stricture and valves. Normally the ureteropelvic junction lies at the most dependent portion of the pelvis and is funnel-shaped. Yet at times insertion of the ureter high on the pelvis results in the equivalent of a functional obstruction. Furthermore, the various types of obstructive lesions may occur in combination; thus when one encounters an aberrant blood vessel over which the ureter courses, a fibrotic narrowing may also be present and require correction.

The amount of renal damage resulting from the obstructive lesions varies from mild to severe according to the duration of the obstruction and the presence or absence of infection (Fig. 10). Parenchymal damage from back pressure is markedly accelerated by superimposed infection.

Symptoms. Though there are no pathognomonic signs or symptoms of the type of hydronephrosis under discussion, the presence of a rounded, movable mass in the renal fossa in an otherwise healthy child is suggestive. An asymptomatic chronic pyuria is also suggestive, as well as unexplained gastrointestinal disturbances and occasionally painless hematuria, particularly after minor trauma. Any of these makes a complete urologic investigation mandatory, at which time the condition is readily apparent. Blunting of the calyces with distention of the kidney pelvis and replacement of the normal funnel-shaped outlet of the kidney by a sharp cut-off or narrowing at the ureteropelvic junction is

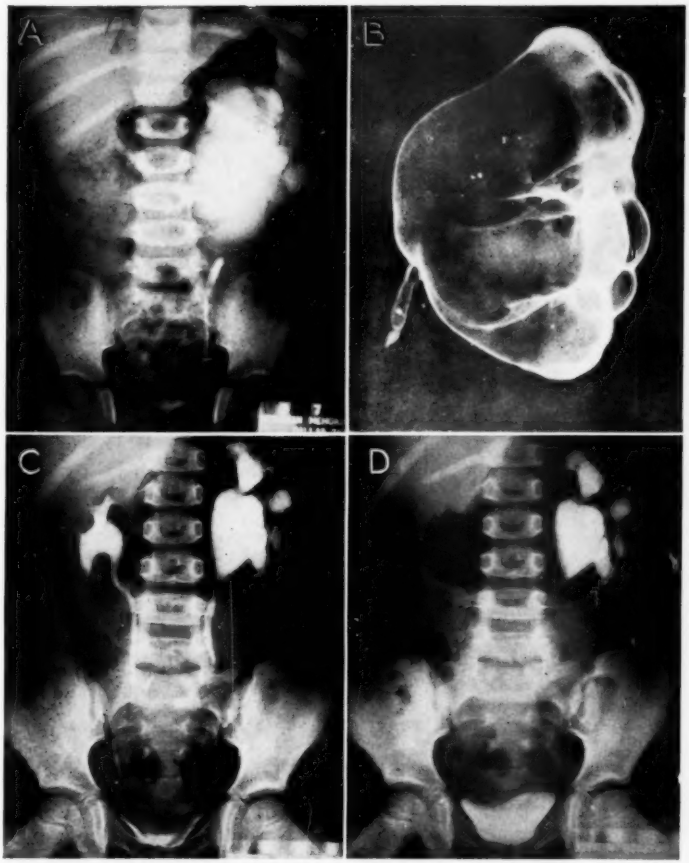

Fig. 10. Hydronephrosis due to ureteropelvic obstruction. *A*, Retrograde pyelogram of destroyed left kidney in a 5 year old boy who entered with large abdominal mass thought to be a Wilms' tumor; obstruction due to aberrant vessel; nephrectomy. *B*, Surgical specimen injected with air showing parenchymal atrophy from long-standing back pressure. *C*, Bilateral retrograde pyelogram showing stricture at left ureteropelvic junction with beginning hydronephrosis. *D*, 30-minute drainage film of same case showing retention of dye above the point of obstruction; successful pyeloplasty performed. Every attempt should be made to diagnose congenital hydronephrosis while the degree of remaining parenchyma permits salvage. (Compare *A*, *B* and *C*.)

diagnostic. Excretory urography with delayed films taken up to an hour or so after injection of the dye often makes retrograde pyelography unnecessary. Since the stirring up of infection by the introduction of a ureteral catheter into the kidney in these cases is quite likely, it is preferable to carry out this examination only when one is prepared to proceed with any indicated operation the next day.

Treatment. In contradistinction to obstructive lesions in the lower ureter, where cystoscopic dilatation is often successful, instrumental dilatation of the inadequate ureteropelvic junction is seldom successful. Best results are obtained by operative relief of the obstructing factors before significant damage has taken place (Fig. 10, *C*). Section of aberrant vessels and plastic procedures to enlarge the pelvic outlet and obliterate stasis of urine all have a place. Diversion of the urine by nephrostomy is often necessary, and in some cases such direct drainage must be maintained for several weeks. The hydronephrotic kidney in children has great recuperative possibilities with adequate drainage, and only when no worth-while parenchyma remains should one sacrifice the kidney (Fig. 10, *A*, *B*). This decision requires nicety of judgment and is based on preoperative studies of function, the status of the opposite kidney, the operative findings and the general condition of the patient. At times removal of an infected kidney in a debilitated child is in the patient's best interest. It is here that teamwork between a urologist interested in pediatric problems and the pediatrician cognizant of urologic principles is essential.

Duplication of the Renal Pelvis: The Double Kidney Problem

Many children investigated for recurrent acute and chronic pyuria will be found to have some variety of duplication of the upper urinary tract. This duplication may occur on one or both sides and may consist simply of a double pelvis with the ureter from each joining shortly after leaving the kidney, or the ureter may be duplicated throughout its course, each ending in the bladder separately (Fig. 11). Some form of duplication of the upper tract is perhaps the commonest anomaly one encounters, and its manifestations are by no means limited to infancy and childhood. Complications are many and varied, chiefly those of obstruction and infection.

The pattern of embryogenesis is such that when the completely duplicated ureters enter the bladder, the orifice to the ureter draining the upper pelvis opens below and medial to that draining the lower pelvis. The ureter to the upper pelvis not infrequently opens in an ectopic location such as into the posterior urethra, the vagina and vulva (Fig. 11, *D*). In complete duplication one of the ureteral openings is often associated with a ureterocele, which has a bearing on the appearance and pathologic changes in the upper tract (Fig. 12). In partial duplication the point of joining of the ureters is sometimes the site of obstruction; when duplication is complete, the ureter to the upper pelvis crosses and recrosses that of the lower so that a functional interference with peristalsis ensues with predisposition to infection.

Symptoms. Recurrent acute pyelonephritis or chronic pyuria typifies

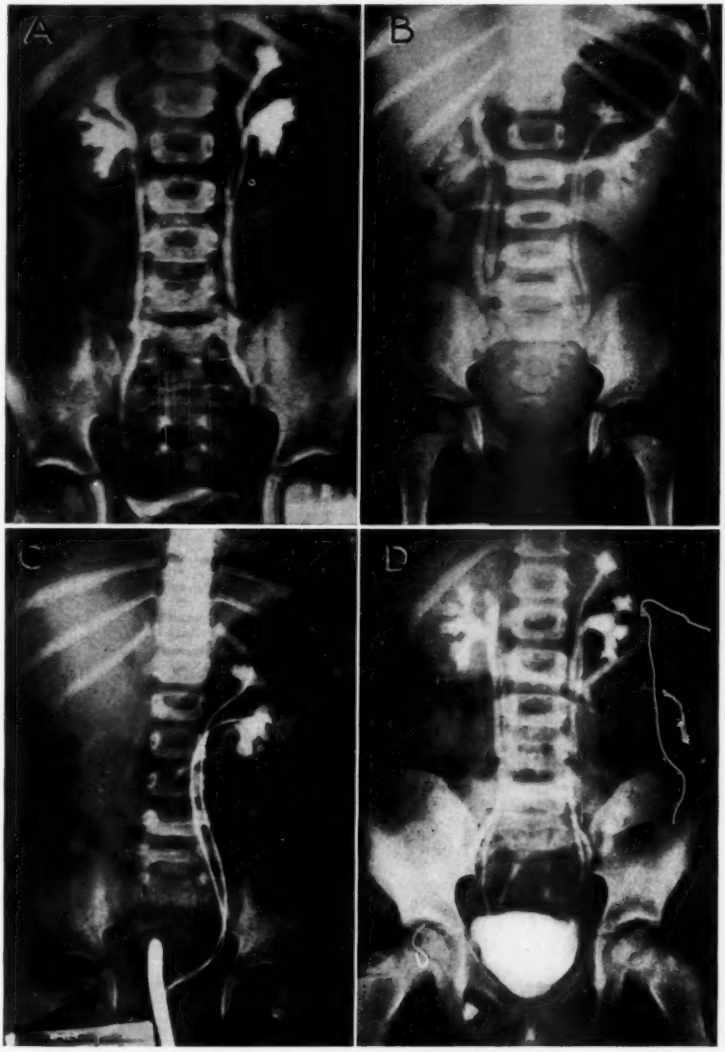

Fig. 11. Pyelograms of various types of duplication of the upper urinary tract. *A*, Unilateral partial duplication—the "Y ureter." *B*, Bilateral partial duplication. *C*, Unilateral complete duplication. (In cases of this sort the findings are usually coincidental and not too important, although occasionally recurrent infection occurs.) *D*, Urologic work-up in a 6 year old girl who had been treated both by spanking and psychotherapy revealed the cause of her constantly soiled underclothing to be an ectopic ureteral orifice draining the upper segment of the right kidney and opening at the introitus distal to the urethral sphincter; cure by removal of upper portion of right kidney; complete duplication of left side also, but here both left orifices opened within the bladder.

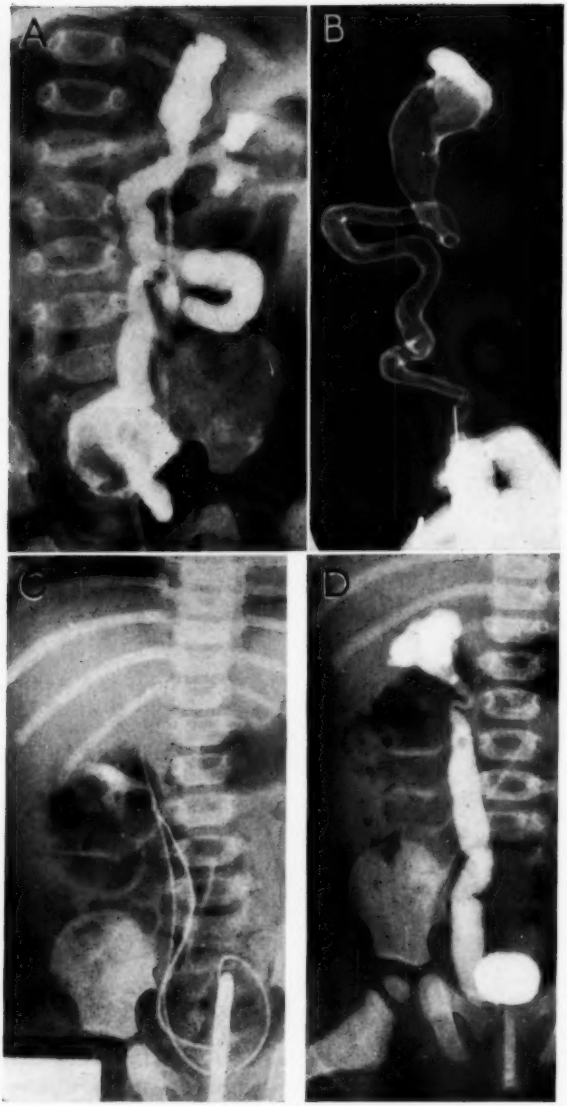

Fig. 12. Urographic findings in 2 small children with history of recurrent pyuria and fever. *A* and *B*, Infected and dilated upper segment of left kidney removed by heminephro-ureterectomy with preservation of substantial amount of parenchyma represented by lower two-thirds of the kidney. *C* and *D*, Similar findings and operative treatment in a small girl in whom the ureter to the upper half of the kidney had an ectopic opening into the urethra. Note remarkably normal appearance of lower portion of kidney. (*A* and *B* from author's article, courtesy Journal of Urology, Vol. 71, Williams & Wilkins, Baltimore, Md.)

the clinical picture in the double kidney problem. Yet the lesion may be completely asymptomatic and occur as a coincidental finding unrelated to the condition for which the patient is being examined. In the absence of infection or urographic evidence of obstruction I am loathe to attribute the explanation of backache or abdominal pain to a double kidney. I have seen many psychoneurotic adults seek refuge in the fact that they have been told they possess "four kidneys" which by no stretch of the imagination could produce the symptoms complained of. Yet I do not mean to minimize the double kidney as frequently being the underlying basis of urinary tract infection.

Diagnosis. A double kidney can be diagnosed in practically all cases by excretory urography. Indeed, this method is often superior to retrograde pyelography when the catheter may enter the collecting segment of only one portion of the kidney. Even when either the upper or lower pelvis fails to visualize on excretory urography, the contour of the one seen is suggestive of the fact that the other must be present (Fig. 12, *C*).

Treatment. In the absence of symptoms or urinary findings no treatment is indicated. In the absence of demonstrable obstruction on urograms, systematic forcing of fluids and combating infection by appropriate chemotherapy and antibiotic agents until a persistently sterile urine is obtained are usually satisfactory. In the occasional instance of disconcerting recurrent infection in the absence of obstruction, I have been inclined to believe that minor interference with drainage not demonstrable by urograms may exist and have cleared up some of these cases by the passage of dilating bulb ureteral catheters to improve drainage.

A goodly number of cases of double kidney will be found to have one segment, usually the lower, entirely normal, whereas the ureter and pelvis to the upper segment are greatly dilated, usually because of obstruction at the ureterovesical junction, ureterocele, and the like. Here heminephro-ureterectomy is an extremely useful procedure (Fig. 12). By this procedure one gets rid of the septic damaged portion of the upper tract and yet saves the normally functioning tissue. Heminephrectomy is likewise the operation of choice to cure a distressing incontinence when one ureteral opening is ectopic (Fig. 11, *D*).

URETERAL ANOMALIES

To pass now to a consideration of anomalies of the ureter, the classification of Campbell is useful (Table 6). From this list I shall discuss the ectopic ureter, ureterocele, congenital stricture at the ureterovesical junction, and "megaloureter."

TABLE 6. *Ureteral Anomalies**

I. OF NUMBER
- A. Agenesis
- B. Duplication

II. OF ORIGIN
- A. Ureteropelvic
- B. Retrocaval

III. OF TERMINATION
- A. Ectopia
- B. Ureterocele

IV. OF CALIBER AND STRUCTURE
- A. Congenital stricture
- B. Congenital valves, folds, twists and kinks
- C. Vascular blockage
- D. Congenital dilatation without obstruction—megaloureter

* Modified from Campbell.[1]

Ectopic Ureteral Orifice

It has been mentioned that the ureter draining the upper half of a duplicated kidney tends to open elsewhere than at its normal site. Occasionally the ureter from a single kidney likewise has an ectopic termination. The symptoms of ureteral ectopia depend upon the location of the opening. Urinary infection often is present (Fig. 12, *C*, *D*). The history of a female who voids normally and yet experiences a slight but constant leakage of urine is pathognomonic of a ureteral orifice ending distal to the urethral sphincter. A typical case is shown in Figure 11, *D*. Here the ectopic ureteral orifice from the upper half of a double kidney opened into the vagina, and the patient was cured by heminephrectomy. There are a few case reports of successful reimplantation of the abnormal ureter into the bladder, but in general this is not indicated. Ectopic ureteral opening in the male is comparatively rare. Incontinence does not occur, but infection is the rule. Here the abnormal termination is usually into the seminal vesicle or the posterior urethra proximal to the external sphincter. Extirpation of the diseased segment of the urinary tract is the treatment of choice.

Ureterocele

A ureterocele may be defined as a cystic dilatation of the intravesical segment of the lower end of the ureter with ballooning into the bladder (Fig. 13). The condition is congenital and probably due to a stenosed "pinpoint" ureteral opening. Papers and case reports attest to its increasing importance as a cause of misdiagnosed "chronic pyelitis" in children. The condition is more common in the female than in the

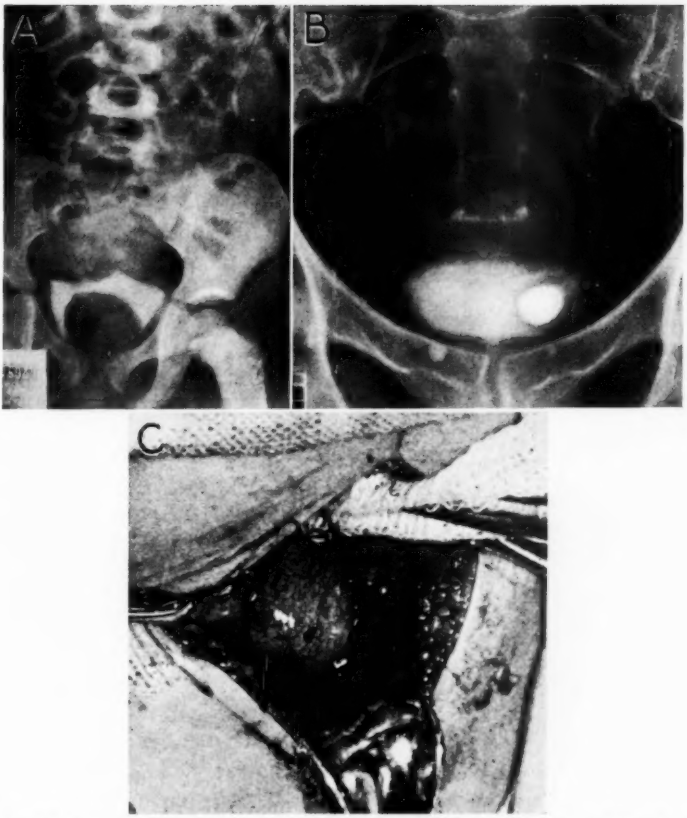

Fig. 13. Examples of ureterocele. *A*, Filling defect in bladder on delayed film in excretory urographic series showing typical massive ureterocele in a girl 3 months of age. *B*, Similar film in adult of ureterocele containing a stone and demonstrating the "halo sign." *C*, Appearance of ureterocele through the open bladder in an infant. In each of these cases the ureterocele represented the termination of the ureter to the upper segment of a duplicated kidney. (*A* and *C* from author's article, courtesy Journal Urology, Vol. 71, Williams & Wilkins, Baltimore, Md.)

male. It is likely to occur in connection with duplication of the upper urinary tract.

The *symptoms* of ureterocele, in addition to chronic pyuria, consist of pain in the abdomen on the affected side due to obstruction, and at times difficulty in voiding when the cyst is sufficiently large to cause partial or complete obstruction of the bladder outlet. In girls the ureterocele may even prolapse through the urethra.

The *diagnosis* of ureterocele often may be made on excretory urograms. If large, that is, a centimeter or so in diameter, a persistent filling

defect may show up on the delayed films after the dye has reached the bladder (Fig. 13, *A*). Even when small, the ureterocele may visualize as a bulbous dilatation of the lower end of the ureter with its wall appearing as a halo (Fig. 13, *B*). On cystoscopy ureterocele presents as a translucent cystic structure in the region where the normal ureteral orifice should be. It may balloon up and collapse as a fine jet of urine is expelled through the stenotic orifice, although at times the ureterocele remains persistently dilated and does not empty. The ureteral orifice, when visualized, appears pinpoint in caliber, yet may be impossible to detect. Another cystoscopic appearance of ureterocele may occur when, with the bladder distended, the thinned-out wall everts, simulating a diverticulum. One should consider the possibility of a ureterocele in every case of duplication of the upper urinary tract when only one ureteral orifice is detected.

Treatment of this condition is aimed at relieving the obstruction and saving the affected kidney whenever possible. Dilatation of the stenotic orifice alone is inadequate. Transurethral incision of a small ureterocele may be successful, but, in general, best results, particularly in children, are obtained by suprapubic excision. Reflux is likely to follow in either case, but in my experience it has been less likely to occur after open operation when suture of the mucous membrane to restore the normal valve action has been carried out. If the kidney is hopelessly destroyed, nephro-ureterectomy or heminephro-ureterectomy in the duplicated kidney cases is curative (Fig. 12, *A*, *B*).

Congenital Ureteral Stricture

Abnormal narrowings along the course of the ureter, interfering with peristalsis and causing variable degrees of obstruction above, are encountered fairly frequently in pediatric urology. The etiology of these narrowings is obscure, but is presumably comparable to that of similar narrowings along the biliary and gastrointestinal tracts. Though the strictures may occur anywhere along the course of the ureter, the narrowings at the ureteropelvic junction, previously described, and at the ureterovesical junction are the greatest in importance.

Here, as anywhere in the urinary tract, an impediment to drainage results in dilatation and ultimate parenchymal destruction above, and predisposes to infection (Fig. 9, *A*). This accounts for the symptoms that we encounter with ureteral stricture, namely, pain from the obstruction, pus in the urine and the systemic manifestations of sepsis.

Excretory urograms often provide the diagnosis. In borderline cases cystoscopy with ureteral catheterization and retrograde films may be necessary to delineate the condition. Difficulty in passing a ureteral

catheter of appropriate size, because of a "hang" or sensation of gripping of the catheter, is confirmatory evidence of ureteral stricture.

Strictures at the ureteropelvic junction, as discussed under Hydronephrosis, are not amenable to ureteral dilatation through the cystoscope, and require surgical relief. Strictures at the ureterovesical junction, however, should have the benefit of repeated systematic dilatation through the cystoscope. Even the comparatively small cystoscopic instruments necessary in small boys will permit passage of dilating catheters sufficiently large to be effective in overcoming lower ureteral

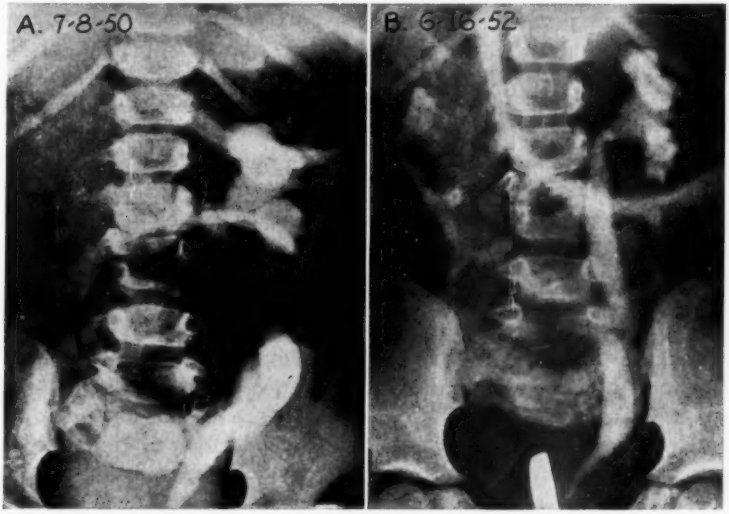

Fig. 14. A, Lower ureteral stricture in 6 months old girl examined for "chronic pyelitis." B, Improved urographic appearance after systematic cystoscopic dilatations; sustained clinical improvement. Note the associated anomalies of the bones.

strictures. In girls larger instruments may be passed with safety (Fig. 14). Since this type of instrumentation, no matter how gently carried out, causes a certain amount of local reaction at the site of the stricture, sufficient time between dilatations should be permitted to allow the resulting inflammatory reaction to clear. It is my practice to carry out the dilatation at monthly intervals, lengthening the time between the procedures as the stricture tends to remain open. The dilatations should be persisted in until the tendency to contraction remains overcome, and the patient is rendered symptom-free with a sterile urine. Repeated excretory urograms are useful in the follow-up of these cases.

When the degree of stricture is such that adequate dilatation cannot be secured by instrumental means, or when the upper urinary tract is massively dilated with elongated and tortuous ureter, or when consider-

able reaction is experienced after an attempt at instrumentation, I believe that open operation on the ureterovesical junction is preferable. The type of operation to be carried out depends upon the lesion present and the surgeon's preference. The objective is to relieve the obstruction and secure drainage without losing the valve action at the junction. Ureteral meatotomy with splinting catheters emerging from a suprapubic wound for two to four weeks is favored by some. Reimplantation of the ureter, the "sleeve pull-through" operation of Campbell, as well as other techniques, are available and may be expected to yield satisfactory results, provided pre-existing damage to the upper urinary tract does not preclude renal recovery.

Obstruction at the ureteropelvic junction due to stricture must be distinguished from the megaloureter due to neuromuscular disorder and from the bilateral hydroureters secondary to bladder neck obstruction. In the latter instance a double lesion may be present in that true ureterovesical strictures may coexist with the bladder neck contracture, yet in most instances the apparent ureteral obstruction here is secondary to the bladder neck condition and regresses after revision of the bladder outlet.

Megaloureter

The term "megaloureter" has been rather loosely used in the urological literature to describe large ureters irrespective of their etiology. Actually, the term was introduced to designate a definite but until recently poorly understood entity, in which massive dilatation of the ureter is found out of proportion to the degree of hydronephrosis and in the apparent absence of obstruction at the bladder neck or ureterovesical junction. An incompetent ureterovesical valve permitting reflux constitutes another feature of the pattern. Much speculation about the etiology of this idiopathic ureteral dilatation has been replaced by the recent work of Swenson, who has presented acceptable evidence that it is a neuromuscular disorder due to a deficiency of parasympathetic ganglia in the lower ureter comparable to his findings in Hirschsprung's disease. At times the bladder musculature may be similarly involved. Absence of normal ureteral peristalsis with its attendant train of ills, chiefly chronic urinary tract sepsis, results. The disorder may be unilateral or bilateral.

The *diagnosis* is made when, on investigating a child with pyuria, cystograms show ureteral reflux and dilatation with no obstructive factor at the bladder neck or ureterovesical junction demonstrable. The ureter in these cases tends to be straight rather than tortuous as in cases of ureteral stricture.

Treatment consists in combating the infection, the use of cholinergic

drugs to produce peristalsis by parasympathetic stimulation and reimplantation of the ureter if, as is usually the case, conservative measures are unavailing. In general, the treatment is less effective than in cases in which remediable organic obstruction is the cause of the dilatation.

SUMMARY

The main congenital anomalies of the upper urinary tract are prone to manifest themselves by recurrent or chronic pyuria, abnormal abdominal masses and atypical abdominal pain, as well as the signs and symptoms of systemic infection. Hence, whenever these are encountered in infancy and childhood, the urinary tract is suspect and the patient should have the benefit of adequate urologic study. Many anomalies can be modified or corrected if discovered in time so that the all-important kidney function may be preserved.

For a more detailed consideration of the various anomalies discussed in this paper, the reader is referred to Campbell.[1]

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1. Campbell, M.: Clinical Pediatric Urology. Philadelphia, W. B. Saunders Company, 1951, pp. 159–253.

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LOWER URINARY TRACT ANOMALIES

JOHN E. HESLIN, M.D.

The close anatomic and embryonic relationship between the urinary and genital systems is a factor in the frequent occurrence of anomalies in the lower urinary tract. Campbell[4] and others state that about 10 per cent of human beings have some such anomaly at birth. The relationship is so close that an anomaly in the genitalia strongly suggests the presence of one in the upper urinary tract in a third of the cases; conversely, in upper tract malformation, two thirds of the cases will show genital anomalies.[4]

The parents of a child with an anomaly are usually greatly concerned about the possibility of such an occurrence in subsequent children. Although the cause of these anomalies may not be known in all cases, studies have been made which aid in giving an answer to these queries. In a review of the subject, including a study by Murphy[5] of 130,132 birth certificates, Campbell concludes that "(a) when a congenital malformation has a genetic basis, there is a greatly increased chance that subsequent brothers and sisters will be also malformed; (b) when a congenital defect is due to factors that are not genetic in origin, offspring conceived subsequently should be congenitally malformed only with the same frequency as is commonly observed in the population at large."

The great clinical importance of anomalies in the urinary tract is the frequent association of obstruction, which, with added infection, may account for early death of the child or a badly disabled urinary tract with decreased function.

Conservation of renal tissue demands that such lesions be discovered and corrected early before serious damage has occurred.

EMBRYOLOGY

Since some of the anomalies have an embryonal basis, a brief survey of the embryology of the lower urinary tract may be of value in this discussion.

The bladder is derived from the *allantois* and the *cloaca*, the former arising from the hindgut of the embryo as a tubelike structure. Adjacent to the allantois the gut forms the cloaca; near their junction the urorectal membrane or fold extends, dividing the cloaca into two parts: the dorsal portion to form the rectum, and from the ventral, or the urogenital, sinus are formed the bladder, the urethra in the female and posterior urethra in the male. Should the urogenital fold or membrane fail completely to divide the cloaca, a *vesicorectal* or *urethrorectal fistula* develops.

In association with a defect in the development of the lower abdominal wall the anterior portions of the allantois may be absent and the bladder floor exposed above the pubis, the *exstrophy of the bladder*.

Into this ventral area the mesonephric ducts are soon to empty, and the dilated allantois and cloaca develop further to form a true bladder. The musculature of this organ appears about the fourth month. Later in development the posterior portion of the partitioned cloaca ruptures to form the anus, and the ventral segment, or urogenital sinus, opens into the future urethra.

The cloaca apparently plays the main part in the formation of the bladder, and the allantois then decreases greatly in size and usually remains as a fibrous cord extending beneath the posterior rectus sheath from the bladder to the umbilicus and is known as the urachus. Failure of this cord completely to fibrose results in patency, or *cyst of the urachus*.

The remaining portion of the urethra is formed with the genital tubercle, which develops into the penis in the male and the clitoris in the female. Upon the ventral surface of the penis a groove is developed which is later closed over and forms the urethra. Here, failure of portions of the groove to be covered gives rise to the various types of *hypospadias*.

The prostate and Cowper's glands are outgrowths of urethral epithelium.

ANOMALIES OF THE URETHRA

EPISPADIAS

This is a rare congenital malformation, 1:30,000, with the urethra, in the male, placed upon the dorsal surface of the penis, above the corpora cavernosa, without an upper covering and opening usually near

the base of the penis. Three forms occur in the male: (a) Balanitic type, the most uncommon, has a defect extending upon the dorsum of the penis from the coronal ridge to the tip of the glans with incontinence usually not present. (b) Penile type has the urethral opening in front of the symphysis with a short, flat, curved penis. Incontinence may be present. (c) Penopubic type is associated with exstrophy of the bladder, and incontinence is practically always present.

The condition is apt to be associated with other anomalies such as exstrophy of the bladder, separation of the pubis, cryptorchism, hernia, or absence of the prostate gland.

Etiology

The cause of this anomaly is not clear. It is probably associated with displacement upward of the cloacal membrane before the genital tubercle has been formed, as suggested by Hinman.

Symptoms

Epispadias in the male, although it may vary in degree, presents a groovelike structure lined with mucosa extending from the meatus to the glans. In the complete type the pubic bones are separated, the entire roof of the urethra is absent, and it blends into an exstrophy of the bladder. The penis is apt to be deformed, flattened and possibly curved upward by the fibrous tissue which has replaced the urethra. The glans is not covered by prepuce. Symptoms are those of urinary dysfunction with some difficulty in intercourse. Excoriation of the skin of the area from leakage of urine or complete incontinence occurs.

Epispadias also occurs in the female with three types described. These are based upon the appearance of the large meatus, the slitlike urethra and the divided urethra and sphincter.

In the absence of incontinence, diagnosis may be delayed until the associated genital deformities are noted. The bifid clitoris, the separation of the labia and pubic bones call the child's attention to the fact that she is not normal and may, in themselves, lead to psychic symptoms.

Incontinence with excoriation and urinous odor will usually lead to investigation, diagnosis and correction.

Treatment

This is surgical, and, because of the frequently associated incontinence, it must provide for not only a new urethral passage, but the control of the urine as well. The correction of the deformity is discussed in the article by Dr. Cecil in this symposium.

HYPOSPADIAS

This is a more common defect, and, if marked, the mother or nurse calls it to the attention of the physician. The urethra ends at a point on the ventral surface proximal to its usual site. A stenosed meatus, a hood effect produced by the prepuce upon the dorsal surface and a downward curvature, distal to the meatus, gives the condition a distinct appearance.

Etiology

Hypospadias is due to a failure in the formation of the distal portions of the urethra, owing to the nonclosure of the urethral groove. Marked cases with a bifid scrotum suggest hermaphroditic relationship. In cases of considerable deformity the deposits of fibrous-like tissue distal to the meatus, between and around the corpora cavernosa, are capable of producing chordee by contracture.

Types

The various types of hypospadias are based upon the location of the meatus and extent of defect.

Balanitic or Glandular. This is the most common type, with the meatus at the frenum. This form, making up 40 to 50 per cent of cases, may or may not have associated deformities of the penis or urethra.

Symptoms are due to any narrowing of the meatus, and this may require dilatation or meatotomy. Failure to deliver properly the ejaculate, because of the location of the meatus upon the ventral surface, has been mentioned as a factor in sterility problems. Innumerable cases would seem to disprove this fact.

Plastic procedures to place the urethra through the glans to give the meatus a normal position are not usually satisfactory and would seem to be not indicated in most cases.

Penile. Here the meatus is at some point between the glans and the penoscrotal junction, usually with a grooved area extending forward to the glans. Associated deformities are more apt to be present in this type. The cosmetic disturbance of the marked hoodlike prepuce, the chordee and the flattened glans, along with the difficulty in propelling the urinary stream beyond the scrotum and failure of insemination, may require surgical procedures to correct.

To have the correction of the chordee at the age of one or two years and to avoid any removal of the hoodlike prepuce, which may later be used in plastic procedures, are two important suggestions for the physician who is caring for these cases.

Penoscrotal. Here the deformities are apt to be more evident, with marked chordee, flattened and deformed glans, meatal stricture and un-

derdeveloped penis which may simulate a clitoris. Other anomalies such as undescended testes may be present.

Perineal. Extreme deformities such as a split scrotum, large open meatus, rudimentary penis, with marked chordee, appearing as a hypertrophic clitoris, give the appearance of a pseudohermaphrodite.

Sex determination may be difficult in advanced cases, and a hasty diagnosis may well lead to later embarrassment. Surgical exploration is at times necessary before the sex can be determined and proper plastic procedures carried out.

Absence of the urethra, double urethra and *accessory urethral canals* are mentioned to call attention to their rarity and do not seem relevant to this discussion.

CONGENITAL MEATAL STRICTURE

This is probably the most common congenital anomaly and, although mentioned as occurring with hypospadias, is also frequently seen in otherwise normally developed urethras.

There is a great variance in the clinical effects of this condition. Many children never have a symptom, while others will present end results of obstruction with damage to the entire urinary tract.

The most common course is based upon a sequence of events initiated by the small meatus with resulting poor urethral drainage, irritation by retained drops of urine, mucoid discharge and infection—further constriction of the meatus, ulceration and possible bleeding as its covering is detached. In some cases this ulceration is said to be due to the irritation of the diaper, but associated evidence of irritation in the surrounding parts should be evident.

These *pathologic changes* will explain the usual symptoms of burning, pain, hesitation, discharge, ulcerated meatus and at times drops of blood upon the diaper or underwear.

Strictures, in the urethra proper, are less frequently seen, but should be regarded, in any urologic investigation in children, as a possible underlying cause of infection, hematuria and obstructive symptoms.

Diagnosis

The symptoms and the small meatus with ulceration and discharge will indicate meatal stricture, while other urethral strictures will require instrumental examination to demonstrate.

Treatment

A *prophylactic measure*, carried out at the time of circumcision, may well prevent future symptoms. Meatal dilatation and possible meatot-

omy when the meatus is constricted will often avoid another admission, anesthetic and operation.

Attention might be called to the importance of examination of the prepuce and meatus in young children who are to operated upon for tonsils, adenoids or other conditions. With short procedures, such local anomalies can be corrected, saving another anesthetic for the patient and expense for the family.

Simple dilatation of the meatus with a small sound with local application of a mild urinary antiseptic fluid may allow better drainage and clearing up of the condition.

Cases not responding to this treatment will require hospital admission, anesthetic and *meatotomy*.

Because of the usual difficulty in carrying out the postoperative measure of dilatation to keep the meatus enlarged, simple incision is apt to produce a more constricted and scarred meatus.

The application of a small "mosquito" forceps to the midline area of the lower portion of the meatus and pressure for a few moments will greatly reduce the amount of bleeding which might obscure the small operating field. By placing small forceps just lateral to this compressed line, the margins are easily controlled and will allow, by eversion of the meatus, after midline incision, the proper application of fine sutures joining the mucous membrane and the outer surface on either side. This will usually provide a good cosmetic effect as well as maintain an adequate meatus.

Strictures of the urethra will require the passage of sounds of increasing size, at intervals, as carried out for similar conditions in the adult.

URETHRAL DIVERTICULUM

This is a rather rare condition usually found upon the floor of the urethra anterior to the bulbous portion. It is apt to be associated with obstruction such as meatal stenosis or stricture of the urethra.

Whereas, in the adult, the diverticulum of the urethra is more often found in the female, Campbell[4] could find no recorded case in infants or children.

Except for the passage of a varying amount of urine after urination, the condition is usually associated with urinary tract infection and discovered in the investigation of such condition.

Diagnosis

As in the adult, diagnosis is made by visualization with the endoscope and urethrographic study. The ability to expel, with local pressure, urine from the urethra will make one suspicious of such an anomaly.

Treatment

Removal of any obstruction distal to the diverticulum and its dissection with plastic closure of the urethra are required.

URETHRAL VALVES

These are congenital folds of mucous membrane in the prostatic urethra, proximal and frequently attached to the verumontanum, which may or may not be enlarged. With the expression of urine from the bladder, these folds tend to balloon up as an umbrella, producing various degrees of obstruction, depending upon their size and amount of constriction. Nesbit, Thirlby and Raper[6] call attention to horizontal flaps of bladder mucosa above the trigone in producing obstruction.

It is difficult to estimate the incidence of this important congenital lesion, since many cases are overlooked, even after careful endoscopic study. They must be ruled out in all studies in which obstructive sequelae are present.

Although considered upon the basis of embryology, with several theories advanced, no definite relationship has been established.

Pathology

These changes result from the obstruction produced, and, if not corrected soon after birth, extreme dilatation of the bladder, the ureters and renal pelves and calyces occurs, leading to complete destruction of the renal parenchyma. Although this extensive damage can proceed with a normal urine, infection usually takes place at some stage, and inflammatory changes are added to those of obstruction. Locally, the folds of mucous membrane then become more prominent and obstructive.

Symptoms

Severity and time of appearance may vary, but if the obstruction is of any great degree, there will be evidence of retained urine and symptoms of poor kidney function soon after birth. In mild obstruction the minor symptoms may not be suggestive until later years or until infection has taken place.

Straining upon urination, the overdistended bladder, producing a mass in the lower abdomen, loss of control of urine due to overflow, and the uremic signs of loss of appetite and weight, nausea, vomiting, diarrhea and constipation are present in the typical advanced case.

The generalized symptoms with a normal urine may make the urinary tract the last place suspected. The damaged urinary tract makes infec-

tion inevitable, and the symptoms of cystitis and pyelitis are added to the picture.

Diagnosis

Definite diagnosis is usually made upon cystoscopic examination, although visualization of the folds or valves in the prostatic urethra is often difficult. A cystogram may suggest obstruction with evidence of reflux. However, the history and distended bladder, with palpable kidneys in the advanced case, indicate distal obstruction, and valves must be considered. Nesbit, Thirlby and Raper[6] stress the importance of observing the voiding of the child to note the straining effort and the small, often interrupted stream. The simple estimation of residual urine, with either catheter or a postvoiding film after urography, may give invaluable information.

Recurrent pyuria, not responding to the present day antibiotics, demands urologic investigation. Fortunately, even these modern drugs are rarely effective in the presence of obstruction, and study leads to its detection and correction.

It is more and more evident that the innocuous procedure of intravenous or subcutaneous urography, when kidney function allows, has possibly its greatest value in cases in which the diagnosis is not clear and findings are inconclusive. Especially in children, in whom early discovery and correction of obstructive lesions are important to save kidney tissue, is the omission of this procedure unforgivable.

Treatment

Transurethral surgery, here, as in the adult, has offered a great contribution. These folds can be resected at all ages with the miniature resectoscope.

Children with markedly reduced kidney function will require cystotomy, and this may be lifesaving. Visualization of the area may confirm the diagnosis, and correction of the condition may be carried out at the time.

Retropubic operation is preferred by Nesbit, Thirlby and Raper,[6] who found examination and excision of the lesion greatly facilitated.

With adequate drainage established and followed by antibiotics, infection is more easily eradicated. Cases with poor renal function, either through marked obstruction at birth or through neglect in investigation, make restoration to normal function less likely; but the natural reserve of the kidney may allow these children years of comfort and good health.

HYPERTROPHY OF THE VERUMONTANUM

Hypertrophy of the verumontanum may also cause obstruction near the bladder neck. Brody and Goldman[3] suggest that estrogens in fetal life, by stimulating metaplasia, may account for a distended utricle and enlarged verumontanum.

Diagnosis, in the marked case, with the verumontanum filling the urethra and extending into the bladder neck, is easily made upon endoscopic examination. However, congestion, associated with masturbation or prostatic infection, and even a normal verumontanum, if not viewed properly, may suggest the congenital lesion, and careful, differential study, aided by urethrogram, should be made.

Treatment

Treatment is usually carried out by transurethral removal of sufficient tissue to allow, after shrinkage, a free urethral passage. Secondary closure of the ejaculatory ducts must be regarded as a calculated risk to prevent progressive damage to the urinary tract. Application of astringent solutions or fulguration may be tried in the borderline case.

CONTRACTURE OF VESICAL NECK

This condition, probably related to the common stenosis of the meatus and less common urethral stricture, is a frequent finding in obstructive uropathy in children. It does not seem to have the definite obstructive effects of urethral valves, just discussed; hence results and symptoms may develop later.

The varying degrees of obstruction and possible delay of symptoms make an estimation of its incidence difficult. Lack of definite evidence of contracture upon instrumental examination, in mild cases, may also play a part in the estimation.

As in meatal stenosis, no embryologic basis seems applicable, but the early occurrence warrants its consideration as a congenital lesion.

Etiology

In the adult, vesical neck contracture is related to infection with secondary fibrotic changes. No such finding can be connected with the initial lesion in the child. In fact, Campbell[4] has shown histologic evidence that these cases do not have inflammatory reaction, and he found submucosal fibrosis and marked muscular hypertrophy present in a few of the cases. The changes may progress to involve prostatic tissue and the trigone, and superimposed infection will add inflammatory products to this picture.

Neuromuscular pathology, producing a spastic sphincter, was men-

tioned by Beer in 1915. Recent work in the obstructive phases of paraplegia indicates that spasm is capable of producing obstruction, and the simple interruption of the sphincter, which tends to relieve it, would seem to confirm the fact.

Symptoms

Symptoms are obstructive and appear at varying times after birth. Difficulty in initiating the stream, because of the contracted internal orifice; dribbling, due to improper drainage; frequent voiding, associated with burning, dysuria, enuresis, hesitation, straining and crying are indicative of this condition. Attacks of pyelitis and cystitis, with recurrence, denote the complication of infection.

Diagnosis

The typical symptoms, physical examination and residual urine estimation will indicate some obstruction, and only a complete urologic survey will give the exact cause and indicated treatment necessary.

Differential Diagnosis

Complete general, neurologic and urologic examination will be necessary to rule out certain conditions giving symptoms of obstruction.

Neurologic lesions with an atonic musculature of the bladder may have a weak stream and residual urine. Cystometric, urographic, cystoscopic and neurologic studies will usually indicate the presence of some such lesion.

Atony of the bladder, associated with primary megaloureter, may be confused with the large bladder and decompensated ureters of obstruction. Swenson and associates[9] have made valuable contributions to the study of megaloureter. They noted the absence of ganglia in the lower ureter and believed that this probably explains the dilatation above. They mention diminution in ganglion cells in the bladder, which may account for the often associated atony of the bladder.

It may be difficult to distinguish definitely between the atony of bladder neck obstruction and this type, but one differential diagnostic point is the dilatation, redundancy and folding of the ureter with a large pelvis found in obstruction and not usually present in primary megaloureter.

Treatment

Transurethral resection has mostly replaced open suprapubic operation and removal of a portion of the contracted bladder neck. This

rather benign procedure followed by measures to eradicate associated infection will stop the progressive changes due to obstruction and conserve remaining kidney parenchyma. The retropubic approach with its direct observation and excision of the neck is now becoming more popular, especially with surgeons who use such a procedure in prostatic surgery.

In advanced cases, when the ureters are dilated, redundant and obstructive, plastic procedures to improve drainage of the upper tract may be necessary to secure maximum return of kidney function.

ANOMALIES OF THE BLADDER

None of these can be termed common, and only diverticulum, exstrophy and urachal cyst will be discussed.

DIVERTICULUM OF BLADDER

As in the adult, obstruction is usually an associated factor. To qualify as a congenital anomaly, this factor must be absent, and there are cases reported in which the diverticulum was found at birth, without obstruction. Whether a congenital weakness of muscle fibers allowing the blowing out of this area or some true embryonic defect, such as patent urachus or lack of fusion of certain elements, is present has not been definitely determined. The literature would suggest that obstruction probably plays an important role, whether the diverticulum is primary or secondary.

Diverticulum of the bladder may be single or multiple, varying in size, lined with mucosa, and occasionally containing the ureteral orifice.

Stagnant urine in the diverticulum leads to stone formation and infection. Dilatation of the ureter and renal pelvis may result when the ureter is displaced by the increasing size of a diverticulum.

Symptoms

These are apt to be those of obstruction or associated cystitis. However, there are two definite symptoms which make one suspicious of diverticulum of the bladder: (1) the passage of a good amount of urine after voiding, as the diverticulum empties, and (2) the passage of an unusually stagnant, foul-smelling urine, suggesting that it has been retained in a separate cavity.

Diagnosis

This is made upon visualization by cystoscopy, demonstration by cystogram, lateral or oblique or intravenous urography. A film taken

after the voiding of the urographic media will give an idea of the amount of retained urine in the diverticulum, and this may be of important clinical value.

Treatment

Cases with no residual urine and a diverticulum which empties may be kept under observation if the associated infection can be cleared.

Most cases giving symptoms will require some surgical attention. With the increased use of the resectoscope for the removal of bladder neck obstruction there is a tendency, except in large, nonemptying sacs, to remove the obstruction by resection and note the results before open operation and removal of the diverticulum is carried out. In skilled hands the orifice of the diverticulum can be enlarged with the instrument, providing more adequate drainage. In the adult, with large hypertrophied prostate, when suprapubic enucleation may be selected, surgical excision of the sac at the time of enucleation or in a first-stage operation would seem to be indicated. Several technical procedures have been used; probably the most popular is the suprapubic approach with extravesical dissection of the sac, facilitated by its distention with gauze or finger from a cystotomy opening. Adherent sacs may prove more difficult, requiring removal of the mucosal lining of the sac, closure of the orifice and adequate retrovesical drainage.

At whatever stage and however handled, removal of any obstruction is a most important part in the cure of a bladder diverticulum.

EXSTROPHY OF THE BLADDER, OR ECTOPIA VESICAE

Fortunately, this serious and most uncomfortable lesion is rare, occurring about once in 50,000 births. Large pediatric services may have several cases, but the average pediatrician or urologist will probably see but an occasional case in many years of practice.

Exstrophy, as the name implies, is an exposure of the bladder floor through an absence of the lower abdominal wall and anterior portion of the bladder. The inverted posterior surface with the ureteral orifices may show varying degrees of extent, inflammatory reaction, incrustation and laceration. The constant bathing of the surrounding tissues with urine causes irritation, and the ever-present urinous odor makes the patient's existence most trying.

Other anomalies are likely to be associated, such as cleft palate and harelip, absence of pubic bones and intestinal defects. Epispadias and deformities of the penis and loss of sphincteric action are more frequently seen.

Etiology

Several theories have been advanced to account for this deplorable condition, but an embryonic basis is most favored. The most recent studies appear to have been made by Patten and Barry,[7] whose work is referred to by Campbell.[4] They presented evidence to show that a series of hypothetical stages in the disturbed development of this region would explain the manner in which these anomalies arise. They began with the primordia of the genital tubercle and were convinced that this initial developmental disturbance placed these paired primordia a little too far caudally with reference to cloacal outlet, and this began a train of events accounting for the exstrophy, epispadias and other local deformities.

Symptoms

Locally, these are associated with the constant leakage of urine and the pain and irritation of the exposed bladder mucosa. Bone changes may give a typical waddling gait. Ascending pyelonephritis with its usual manifestations is a serious complication and eventually causes the death of the patient.

Diagnosis

This is easily made by inspection.

Prognosis

Campbell[4] states that the great majority of untreated patients die before the age of 21, one half will die in early childhood, and two thirds are dead by their tenth year.

With the improved plastic surgical procedures, anesthesia, transfusions and antibiotic therapy, surgical correction of the condition gives an increasing chance of survival to adult life.

Treatment

Ureterosigmoid transplantation and closure of the defect have formed the basis of surgical treatment, but, because of the upper urinary tract complications following ureterosigmoid transplants, other surgical procedures have recently been advanced.

Sweetser, Chisholm and Thompson[8] have used techniques, suggested by Burns and Dees, of repositioning of the bladder and closure of the abdominal wall and urethra. This two-stage operation, best carried out at six and 18 months, avoids complications of the former procedures.

Boyce and Vest[2] transplanted the trigone of the bladder to an isolated portion of the rectosigmoid after a permanent colostomy. The normal function of the ureteral orifices is maintained, and they believe that this is of sufficient importance to recompense for the colostomy. The rectum serves as a continent bladder, and the closed urethra will allow, it is believed, ejaculation.

CYST OF THE URACHUS

This is a rare anomaly, due to the failure of the allantois to become obliterated. The canal forms a cyst filled with an exudate.

This condition is more common in the male, and varying degrees are found: closure of the tract except for a bladder opening, an umbilical opening, patency throughout its course and closure at both ends with an open midportion. Begg[1] has demonstrated that the adult urachus is potentially patent in one third of all persons and states that many believe that either mechanical or neurogenic obstruction to the outflow of urine from the bladder plays a causative role in the formation of cysts of the urachus.

The size of the cyst will vary from the small unrecognized type to those of great size, simulating abdominal tumors.

Symptoms

Symptoms develop from pressure of the enlarging cyst or from the development of infection with resulting local signs of abscess. The location of the urachus, beneath the rectus and involved in the peritoneum, explains the abdominal symptoms sometimes seen. Persistent drainage from the umbilicus may occur, and cases are reported of discharge into the bladder.

Diagnosis

The fact that the cyst may simulate intra-abdominal lesions may make diagnosis difficult and surgical exploration necessary.

Treatment

Excision of the cyst is the indicated treatment.

PATENT URACHUS

This is another rare anomaly and is also associated with failure of the allantois to be obliterated and completely closed.

With the duct open, leakage of urine from the bladder may be noted

at the umbilicus. Identification of the umbilical drainage can be established by chemical analysis or the administration of dyes.

Bladder diverticulum, when occurring in the dome of the bladder, is suggestive of a patent urachus.

Diagnosis

Discharge from the umbilicus should make one suspicious of a patent urachus, and probing or injection of dye or radiopaque material may aid in making a definite diagnosis.

Treatment

Cases presenting symptoms of any degree and not responding to probe and injection will require excision.

SUMMARY

Anomalies of the urinary tract when associated with congenital defects are of great concern to the parents and require full discussion and advice.

Because of obstruction and its destructive effects, early recognition is obligatory to prevent damage to the upper tract.

Improved plastic procedures and antibiotic therapy have resulted in a better prognosis in the surgical correction of these conditions.

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HYPOSPADIAS AND EPISPADIAS

Diagnosis and Treatment

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The term "hypospadias" implies a male deformity. The so-called female hypospadias is a rare condition which has had various genetic explanations, among which is that it is due to a failure of descent of the vesicovaginal septum with retention of the urogenital sinus, or that it is of traumatic origin.[8]

HYPOSPADIAS

Differentiation from Pseudohermaphrodism in the Female

One of the greatest responsibilities resting upon the pediatrician is a differential diagnosis between female pseudohermaphrodism and male pseudohermaphrodism, or perineal hypospadias. Moore, Graham and Barr[21] recently carried out some studies upon the determination of chromosomal sex by the study of cells obtained by skin biopsy. They found a difference in nuclear structure according to sex in cells of the malpighian layer of the epidermis. Nuclei of female specimens contained a mass of sex chromatin which is seldom seen in nuclei of male specimens. The X chromosomes of the female produce a chromatin mass sufficiently large to be identified, while the X and Y chromosomes of the male fail to produce a chromatin mass of sufficient size to be distinguished from the general particulate chromatin. They conclude that the potential importance of the skin biopsy technique lies in the possibility that it may prove to be a simple method of detecting the dominant sex in infancy in cases of doubt.

In a subsequent paper, Barr[1] discusses the application of the skin

biopsy tests of chromosomal sex to hermaphrodites. He points out that, though the great majority of female pseudohermaphrodites are of the congenital adrenogenital syndrome, not all are, that other factors than the fetal adrenal cortex may bring about female pseudohermaphrodites, and that in these cases there may be either female or male type nuclei: the presence or absence of the female chromatin mass. Barr concludes, from a preliminary study of hermaphrodites, that the skin biopsy test is a useful aid in the differential diagnosis between the congenital adrenogenital syndrome and male pseudohermaphrodism, when the clinical findings are equivocal. However, as pointed out, since not all female pseudohermaphrodites are of the adrenogenital syndrome, and since those which are not may have male or female type nuclei, as judged by the presence or absence of the female chromatin mass, then sex determination by a skin biopsy is not absolutely certain, which brings us back to what I have long advocated, that a biopsy of the gonads should be done as shortly after birth as feasible, within a few hours. Parenthetically, if the baby is found to have ovaries, the clitoris should be amputated at once and the mother told that she has a girl baby. If testicles are found, the mother should be told that she has a boy who has hypospadias that can be cured when he is four years old.

This determination depends upon biopsy of the gonads alone, and not upon the demonstration of a vagina, uterus and tubes, since Howard[20] has pointed out that a high degree of feminism with a well developed vagina, uterus and tubes does not necessarily indicate a gonadal female, for these organs are present to varying degrees and associated with varying degrees of hypospadias, being most developed in cases in which there is perineal hypospadias.

Surgery of Hypospadias

General Considerations. Every stage of surgery of hypospadias is an important procedure. No surgeon should undertake any step in the treatment of hypospadias who is not thoroughly familiar with the operative procedure. An able surgical assistant is absolutely necessary. Any of the operations can be extremely trying and, without good assistance, become slow and bunglesome. Proper instruments and sutures should be laid out with care beforehand. Nursing is best done by the mother, and all unnecessary nursing such as routine bathing, changing of sheets, taking temperatures, and so on, should be dispensed with. The child should be allowed to leave the hospital and go home at the earliest possible time. In the first-stage operation, confinement to bed is not necessary at any time except to recover from the anesthetic. A child rests much better in its mother's arms.

Surgery of the Ventral Curvature. This operation should be done when the child is two and a half years old. Campbell[7] prefers one year

of age. The object is to bring about a full extension of the penis by freeing it from any hindering skin or fibrous bands that keep it in ventral curvature. The operation should be done early in order that the ventral blood spaces of the corpora cavernosa might fully develop. The exact technique of the correction of the deformity necessarily is variable because of the varying deformities found in hypospadias. I do not believe in the transplantation of the foreskin to the ventral surface of the penis. It is unnecessary, and loose redundancies are left which are difficult to work with in the urethroplasties which I shall discuss.

The steps of the procedure for the cure of ventral curvature of the penis are as follows:

POSITION ON OPERATING TABLE. The patient should be in a modified gynecologic position, the thighs and legs flexed and adducted, the thighs to be supported on the outer sides by rolls of blankets or covered with sandbags, and the soles of the feet resting flat on the table and supported by adhesive tape.

PREPARATION. This is done with soap and water and with aqueous Zephiran solution 1:1000. No gauze and no scrubbing are required. Use cotton pledgets lightly.

INSTRUMENTS. A regular dissecting set is used. The sutures are 000 circumcision plain catgut on atraumatic cutting needles with a ⅜-inch circle, as supplied by Davis and Geck (code #635). These sutures are used throughout the first stage of the operation. Three-zero (000) plain catgut is used for ligatures. No nonabsorbable suture should be used in the first stage of the operation. The surgeon and assistant should have stools.

TECHNIQUE. (1) Seize the glans penis with a towel clip.

2. Seize the tissues just in front of the hypospadias meatus with a small clamp.
3. Have the assistant put tension on both clamps. Make a ventral midline incision.
4. Free the skin laterally with dissecting scissors and well forward into the foreskin.
5. Bend the penis back over the hand and dissect out all hindering fibrous bands that hold the penis in ventral curvature.
6. Make lateral incisions on each side, along the coronal sulcus, and open out the lateral portions of the foreskin.
7. Make such lateral nicks in the skin as are necessary to lengthen it, so that it will freely come togther ventrally when the penis is fully extended.
8. Suture the skin with interrupted 000 plain catgut.
9. If there is tension after suturing, make a dorsal linear incision to relieve it.
10. Wrap the penis with an opened-out gauze sponge and fix with adhesive tape, leaving the glans penis to be seen, in order to judge the blood supply. It is not necessary to strap the penis up over the abdomen, nor to suture it there, and it is not necessary to put in a retention catheter.

POSTOPERATIVE CARE. A certain amount of sedation may be required the first night postoperatively. For this I have used 1/16 grain of morphine every six hours, and a Nembutal 1-grain rectal suppository at night. As a rule the child will urinate without any trouble, but if difficulty is encountered in the way of retention of urine, usually a somewhat larger dose of Nembutal will result in the boy's urinating during his sleep. Erections are of no consequence in children.

The postoperative care should be as simple as possible. The mother may take up the child at any time to comfort it. If the dressings become wet with urine, they must be changed. It is not necessary to remove the inner layers, which will be stuck. The child may be put on the toilet. Any diet desired is given. No antibiotics are necessary at this stage, and the child should be allowed to leave the hospital as soon as he has recovered from the operation, usually the next day. It is best not to remove the bandage completely for about six days. If one does, the resulting edema may tear out the sutures.

Two years must now elapse before building the urethra.

The Urethroplasty. For an extensive review of the literature on

the cure of hypospadias, I would refer the reader to my articles in *Transactions of the American Association of Genito-Urinary Surgeons*,[9] and to Cabot's *Modern Urology*[10] and Campbell's *Urology*.[13] Other articles are those by Young and Benjamin,[23] Browne,[2, 3, 4] Havens and Black,[18] Davis,[15] Smith[22] and Havens and Litzow.[19] I have chosen to use the Cecil operation and the Denis Browne operation, both of which I shall describe.

There are four technical essentials for the construction of the urethra in hypospadias: (1) lack of tension; (2) a strip of undetached skin running from the hypospadias opening to the tip of the penis; (3) broad bearing surfaces; (4) diversion of the urinary stream either by external urethrotomy or by retention catheter as advocated by Culp.[14] Of these four essentials, the one absolute requirement in the construction of the urethra is lack of tension. It was formerly thought that the breaking down of the urethroplasties was due to blood clots or infection. Of course a gross hematoma can cause sloughing through of the skin, but ordinary oozing while one is operating is of no importance, and the operator must learn to work in a fairly wet field. Spurting vessels are ligated.

No properly constructed urethroplasty should require postoperative dilatation, nor should the stay in the hospital, as a rule, exceed ten days. On the other hand, the skin sutures in both the Cecil and the Denis Browne operations should not be removed under nine days. The perineal drainage tube is removed at the same time. As to the relative values of the Cecil operation and the Denis Browne operation, if a scrotum is present, I believe that a more certain result will be obtained with the Cecil operation. It does, however, require one more stage than the Denis Browne operation.

Culp, writing from the Ford Hospital and the Mayo Clinic in 1951, has this to say:

> Since 1935 . . . we have attempted correction of a large number of such cases [hypospadias], have run the gamut of operative procedures and have shared the headaches and heartaches of postoperative fistulas, strictures, infections and bizarre deformities.
>
> Our results during the past 4 years with an operation devised by Cecil have promoted enthusiastic endorsement of this 3-stage procedure. Absence of postoperative complications and the adaptability of the technique to patients of all ages have made it our operation of choice. . . .
>
> We have used Cecil's operation (with slight modification) for constructing the urethra in 19 of our patients. It has eliminated fistulas entirely. . . .[14]

Among the cured cases reported by Culp were five patients who had had two or more failures in the construction of the urethra, and one who was cured after nine previous operations.

Campbell[7] states: "Cecil's (1951) modification of the Bucknall operation is fully as satisfactory as the Browne procedure and in my hands more foolproof." It is almost impossible to damage this operation. I

have had cases in which urine and even pus exuded out of the line of sutures between the penis and the scrotum, and yet a perfect result was obtained. Culp also has had instances in which urine escaped along the line of sutures without fistulas.

In each of these operations it is necessary to begin the operation by diverting the urine by external urethrotomy. Culp has extensively used, for the diversion of the urine, an indwelling catheter in the Cecil operation. However, I prefer perineal drainage, and in the Denis Browne

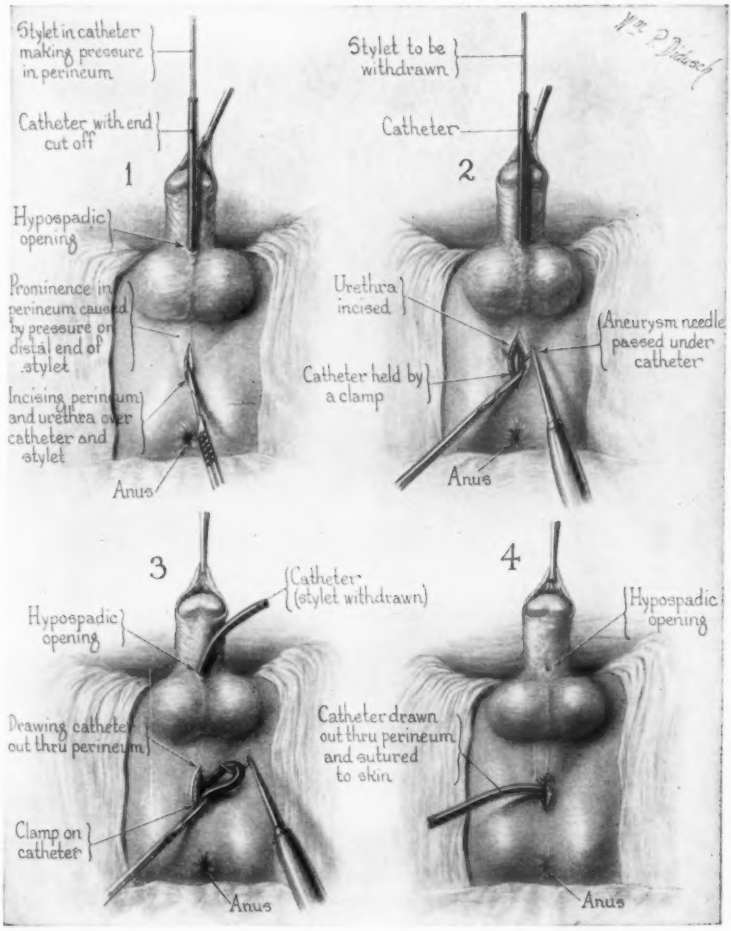

Fig. 15. Hypospadias. Urethrostomy. (Author's article in Campbell: Urology, Vol. III.)

operation perineal drainage is a part of the procedure. In both operations external urethrotomy is done by a method first described by me.[11]

This consists in passing a number 16 Foley catheter through the urethra into the bladder, for a considerable distance, so that the catheter is curled up in the bladder. Now, a straight stylet, about 8 inches in length (I use a bone pin), is passed down through the catheter so that its tip within the catheter can be used to make the catheter prominent in the perineum. Having cut down upon the catheter, the stylet is used to lift the catheter into the wound, which is then grasped with a pair of forceps to keep the proximal end of the catheter from being pulled out of the bladder. The distal end is caught by a pair of forceps and pulled out of the perineum from the external urethra. To do this it is advisable to cut off part of the funnel tip of the catheter. The object in

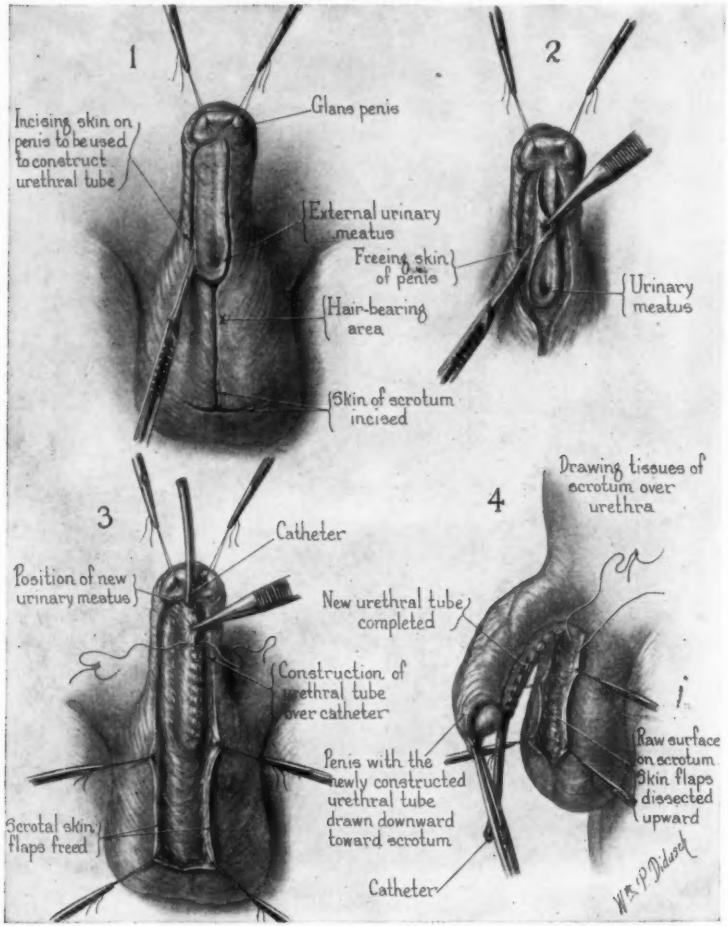

Fig. 16. Cecil urethroplasty. (Author's article in Campbell: Urology, Vol. III.)

using a straight stylet is that it is easily introduced and, more important, easily removed. When the distal portion of the catheter has been drawn out of the perineum, the excess length of the catheter which was curled up in the bladder, in order that a short, straight bone pin might be used as stylet, is now drawn down until the bulb engages the neck of the bladder (Fig. 15).

The size of the drainage tube is important. Denis Browne used a Malecot catheter and fastened it in by suturing it both to the perineal wound and to the thigh. I prefer

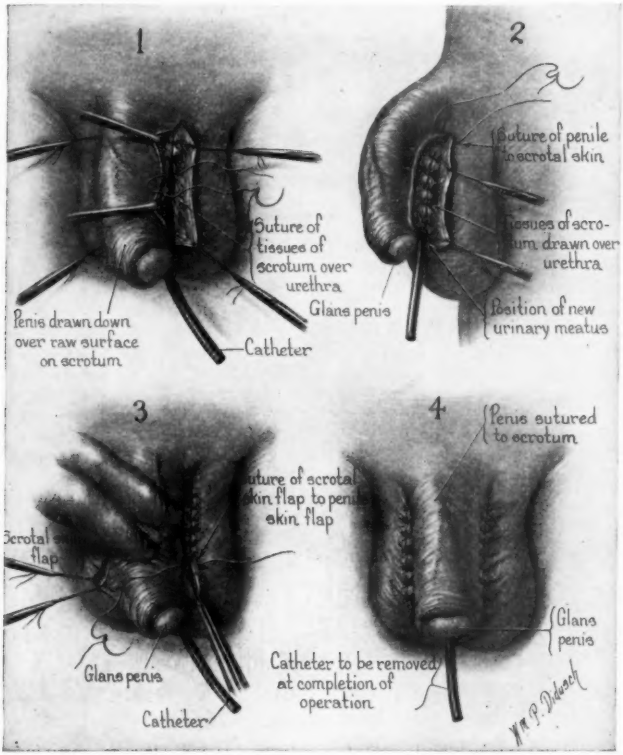

Fig. 17. Cecil urethroplasty. (Author's article in Campbell: Urology, Vol. III.)

to use a number 16 Foley catheter, which can be easily introduced into a four and one-half year old child. The catheter is connected to a bottle under the bed by means of a plastic tube of the same size as the catheter. Should the child have any distress, it will be advisable to disconnect the catheter from the tube, since this procedure will often allow the bladder to empty when it would not otherwise do so, probably because of stoppage of the eye of the catheter by the bladder wall.

The Cecil Operation. The operation which I devised is a modification of the Bucknall[5] operation. The Bucknall operation (1907) had much in its favor, but there was one fault, namely, that in using the skin of the scrotum to form a part of the urethra, hair grew into the urethra

and calculi formed on these hairs. It occurred to me that it was not necessary to use any skin from the scrotum whatsoever, and so I devised an operation in which the urethra was formed from the skin of the penis, and this was then buried in a midline incision in the scrotum.

The steps of the procedure for the Cecil operation are as follows (Figs. 16, 17, 18):

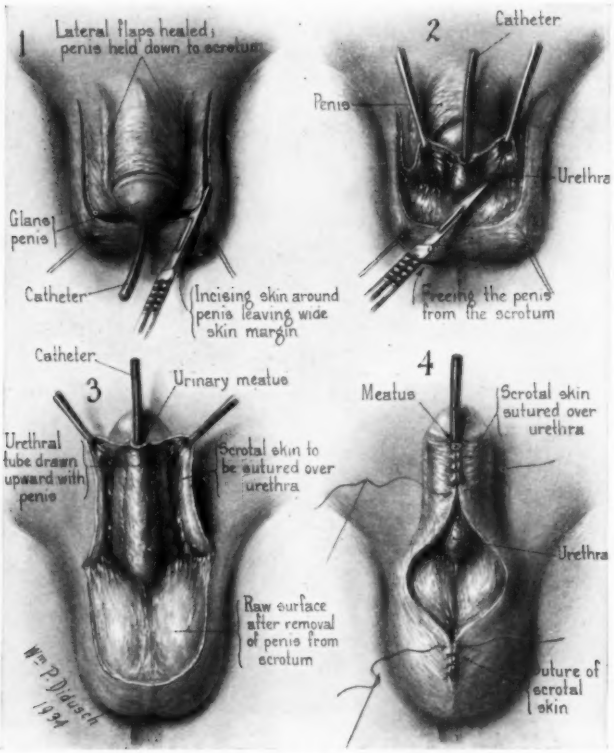

Fig. 18. Bucknall operation for hypospadias. Separation of penis from scrotum; closure of ventral penis. (Author's article in Campbell: Urology, Vol. III.)

POSITION ON OPERATING TABLE. This is the same as described for the first-stage hypospadias operation.

PREPARATION. This is the same for the first-stage hypospadias operation.

INSTRUMENTS. A regular dissecting set is used. In addition, there will be required a number 16 Foley catheter, a 5-cc. bag and syringe for inflating the catheter bulb, an 8-inch straight bone pin, a number 12 French soft rubber catheter over which the urethra is to be constructed, 000 plain catgut for ligatures, regular circumcision plain catgut 000 on atraumatic cutting needles with a ⅜-inch circle as supplied by Davis and Geck (code #635) (this suture is used for constructing the urethra and for suturing the penis down to the scrotum). In addition, Dermalon nylon 000 with atrau-

matic needles, as supplied by Davis and Geck (code #1683), is used for interrupted sutures in approximating the penile skin to the scrotal skin. Sulfanilamide powder is used as dressing. A drainage bottle is to be ordered for the room when the patient returns from surgery. The surgeon and assistant are to have stools.

TECHNIQUE. (1) Perform an external urethrotomy as described earlier.

2. Seize the glans penis with a towel clip.

3. Make incisions for the formation of the urethroplasty, as shown in Figure 16.

4. With a running suture of 000 plain catgut construct a urethral tube over a number 12 French soft rubber catheter. The catheter is removed after the urethra has been constructed.

5. With continuous 000 plain catgut, suture the penis to the scrotum.

6. With interrupted Dermalon nylon, suture the skin of the penis to the skin of the scrotum.

7. Dust the region with sulfanilamide powder.

8. Enclose the penis and scrotum in gauze as one dressing to bring about immobility.

POSTOPERATIVE CARE. Connect the drainage tube to the bottle. For sedation give 1/16 grain of morphine every six hours if necessary; at night, 1-grain Nembutal rectal suppository. The diet may be any desired. Administer a Combiotic injection once a day of 0.25 gm. of dihydrostreptomycin with aqueous penicillin G procaine, 150,000 units (one half of a Combiotic bottle, as supplied by Pfizer). Replace the dressings about the third day. The dressings should be cut away from any gauze that might be stuck to the line of suture. No drugs are necessary to combat erections in children of this age. Sutures and drainage tube are removed on the ninth day. This should not be attempted without a general anesthetic. Magnifying glasses are helpful.

In three months the penis may be freed from the scrotum. Care must be taken not to cut into the urethra. This operation also must not be taken lightly, since it can be very trying because of oozing of blood. When there is considerable tension, doubly locked sutures should be used rather than loop sutures. It may be necessary also to make one or more incisions to relieve tension at the penoscrotal angle. The sutures may be removed on the ninth day. A general anesthetic is required. As a rule I have used a preliminary external urethrotomy.

The Denis Browne Operation. Denis Browne[2, 3, 4] recently revived an operation that was first described and illustrated by Duplay in 1880[16] and again in 1886,[17] and was reviewed by me in 1936 in Cabot's *Modern Urology*.[10] Duplay first originated the idea that a strip of skin left on the ventral surface of the penis, not made into a tube, would, when enveloped by broad-bearing lateral flaps, develop a urethral tube. He pointed out the value of broad bearing surfaces in wide dissection of the lateral flaps. He used single sutures which were doubly locked, the single sutures not cutting holes as would loops, and sutured the skin edges with fine catgut. He mentioned a dorsal relaxing incision. Duplay reported five cases he had cured by this method. Burns[6] reported a series of cures in which he used the Denis Browne operation.

Denis Browne uses a modification of my method for doing external urethrotomy, which I had previously described. The changes which Denis Browne made were as follows: the use of a curved stylet in the urethral catheter, the use of a Malecot catheter instead of a Foley catheter, and making the perineal incision with a diathermy knife instead of a scalpel. All these changes are open to criticism. One cannot

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place a Malecot catheter as accurately as a Foley catheter. The catheter is sutured in rather than held by a bulb, which was largely the reason for the development of the Foley catheter. Secondly, a curved stylet is difficult to get in, more difficult to get out. Thirdly, a diathermy cutting knife does not control bleeding, and makes healing of the perineum wound much slower, so that the perineum wound does not immediately close as it does when one uses a knife.

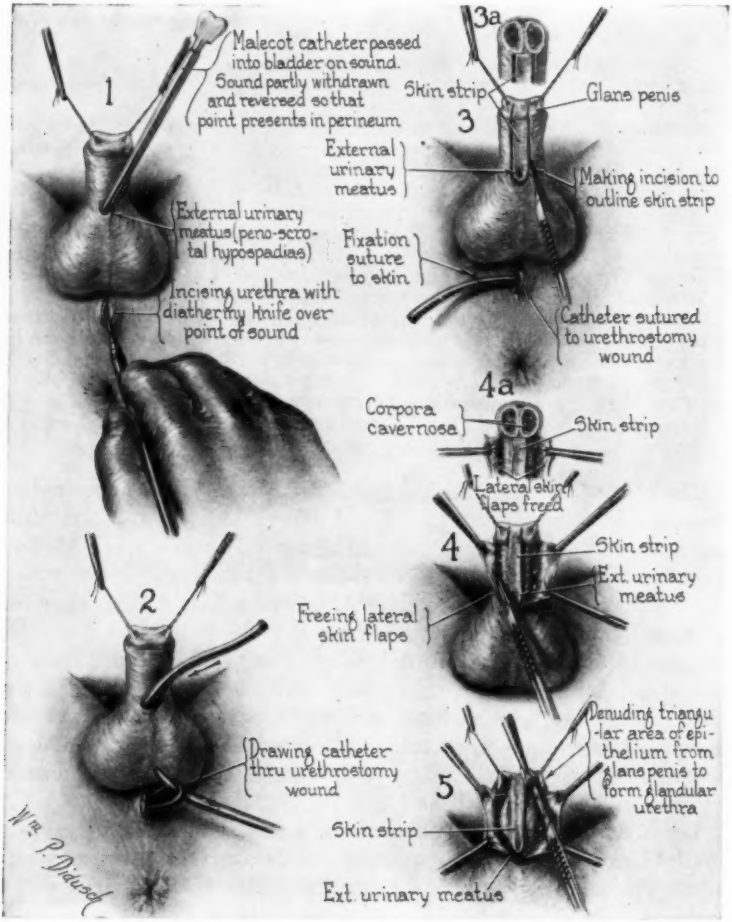

Fig. 19. Hypospadias. Correction by Browne procedure. (Figures 19 and 20 drawn and amplified after line sketches furnished by Mr. Denis Browne. From Campbell: Clinical Pediatric Urology.)

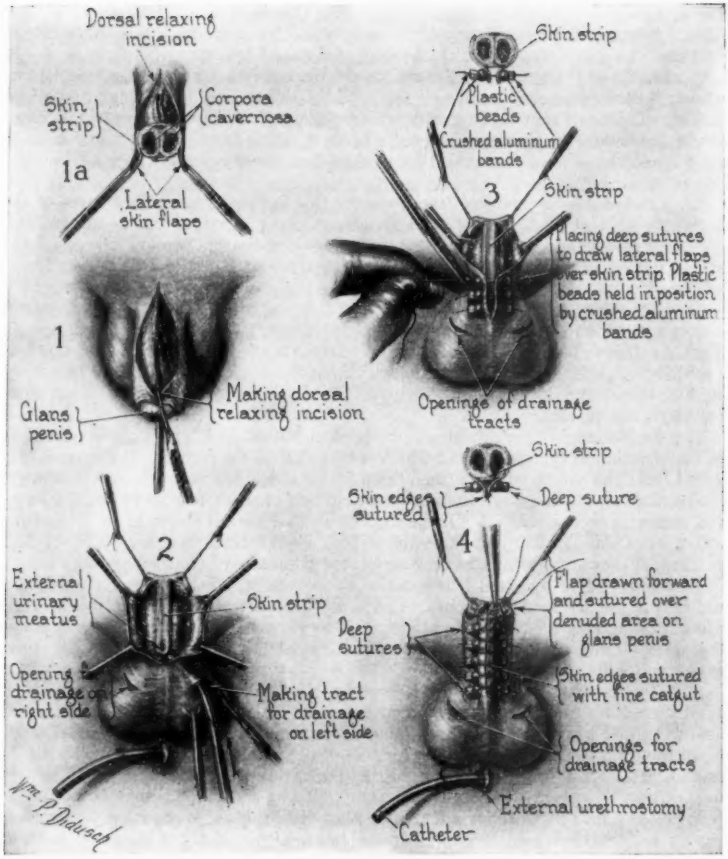

Fig. 20. Hypospadias. Correction by Denis Browne procedure. (Author's article in Campbell: Urology, Vol. III.)

The steps of the Denis Browne procedure are illustrated in Figures 19 and 20. I shall quote from Denis Browne's article on this operation.*

The skin flaps are raised up widely on either side by divulsion with blunt scissors, so that they can fall together quite loosely with about an inch to spare; there must not be the slightest suspicion of tension on the joining flaps. A considerable amount of haemorrhage occurs during this process, but I think it is inadvisable to ligature any but large and obvious bleeding points. Attempts to gain a perfectly dry field waste time and are apt to fill the wound with catgut and damaged tissue. I have never known the bleeding to cause anxiety.

. . . *The relaxation incision.* To get the complete relaxation that has been mentioned it is necessary to take full advantage of the mobility and extensibility of the penile

* By courtesy and permission of Mr. Denis Browne and The Postgraduate Medical Journal.

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skin by means of a longitudinal dorsal slit. . . . This is spread widely open . . . and allowed to epithelialize spontaneously, a process which . . . occurs rapidly and easily in the penis in a way that suggests the healing qualities of mucosa rather than skin.

In addition to doing away with tension, this incision has another function in preventing the excessive oedema, which is one of the difficulties of the region, by allowing free outflow of serum. To guard against oedema in the scrotum small incisions should be made with the sharp-pointed scissors, running from the inner raw surfaces out through the skin. . . . No drains are used in these small holes and they heal rapidly and automatically.

. . . *Tension sutures for the lateral flaps.* All that is necessary for the success of the operation is to get a junction of the skin edges along the ventral line of suture. This will occur rapidly and soundly inside a week, provided that all tension is kept off the edges, that no urine is allowed to burst them apart and that they are adjusted with extreme accuracy.

After many experiments I have worked out a device which I have found very satisfactory for this and other operations in which tension has to be kept off joining skin edges. I call it the 'double stop' suture. It is a variant of the ancient trick of crushing a split shot or lead bead on the suture, which has the obvious advantage of not grasping any tissues and so interfering with the blood supply to the healing edges as do ordinary deep sutures.

The double stop suture consists of one bead or button which goes against the skin, and an aluminium cylindrical bead which is threaded on the suture to the outer side of it and locks the suture when crushed upon it. To crush it a very efficient instrument can be made by cutting down the jaws of an old pair of artery forceps to about a ¼ in. and removing the catches. . . . These stop sutures are placed about ½ in. away from the edges of the skin flaps, and adjusted so that when locked there is a ⅛ in. of slack in them. If they are drawn tight they may cause sloughing where their pressure comes.

To remove them one cuts between the two beads, which has the advantage that the skin is not touched and consequently very little objection is made by the child when they are taken out. Even lightly applied stops may sink into the tissues in a way that makes it difficult to cut between them and the skin, particularly in a very sensitive region and with a young patient.

. . . *Joining the skin edges.* This is done by the smallest possible catgut sutures applied with the utmost care, to avoid inversion or maladjustment. When the whole ventral surface of the flaps has been joined, it is then lifted upwards and sewn to the tip of the glans so that the raw under surfaces of the penile skin are in contact with the raw surfaces produced on either side of the new meatus.

. . . *After treatment.* If there is any oozing after operation, this may be controlled by a pad and firm pressure for a few hours, but after this the wounds are left open to the air with no dressing but sulphonamide and penicillin powder blown upon them. The stop sutures are removed after seven days and the urethral catheter after a week; the child is then allowed to get up. It is perhaps necessary to give a warning to those unfamiliar with operations of the kind that the oedema and the large bare area on the dorsum of the penis make the immediate post-operative appearance in many cases rather alarming. They may be consoled with the assurance that the healing processes will restore the normal outline in the most astonishing way in the course of a few weeks. Along the line of the new urethra there is for about a year a steadily diminishing thickening in the subcutaneous tissues; this finally disappears and the tissues become supple and elastic.[2, 3]

The steps which I have used in doing the Denis Browne operation are as follows:

POSITION ON OPERATING TABLE. This is the same as previously described for the first-stage hypospadias operation.

PREPARATION. This also is as previously described for the first-stage hypospadias operation.

INSTRUMENTS. A regular dissecting set is used. In addition, there will be required a

number 16 Foley catheter; a syringe to inflate the bulb; an 8-inch straight bone pin; number 12, 14 and 16 French curved sounds; 000 plain catgut for ligatures; regular circumcision plain catgut 000 on atraumatic cutting needles with a ⅜-inch circle, as supplied by Davis and Geck (code #635) (this suture is used for approximating the outermost skin edges); Dermalon nylon 000 with atraumatic needles, as supplied by Davis and Geck (code #1683), for the through-and-through lock sutures; 20 lettered beads, as used in the obstetric department; aluminum clips for locking the beads in place (for this I have used small aluminum tubing which may be obtained from model locomotive stores and sawed across with small razor saws, which are also to be obtained in these stores); and an instrument for crushing the aluminum clips.

The surgeon and assistant should have stools. There should be two clean surgical nurses in order that the sutures might be rapidly handled.

TECHNIQUE. (1) Perform an external urethrotomy, as described earlier.

2. Seize the glans penis with a towel clip.

3. Make incisions for the formation of the urethroplasty, as shown in Figure 15. Continue as described in Figure 16.

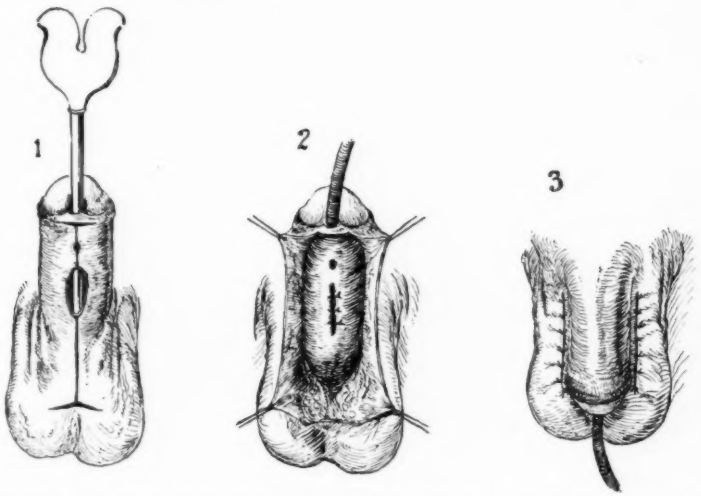

Fig. 21. Cecil operation for urethral fistulas. (Author's article in Campbell: Urology, Vol. III.)

I have never found a scrotal incision of value in reducing edema, and have, in recent operations, omitted it with no harm to the operative procedure. I must emphasize, in this operation, that the doubly locked sutures should have at least ⅛-inch play in order that when the edema occurs they will not cause sloughing through the skin.

Treatment of the Vagina in Perineal Hypospadias. When a vagina has been demonstrated in perineal hypospadias, the proper treatment consists in construction of the urethra with the urogenital sinus opening into the urethra. No attempt should be made to remove the vagina in these cases, since it remains collapsed and offers no discomfort whatsoever.[12]

Urethral Fistulas. No study dealing with the cure of hypospadias is complete without a consideration of the method for curing urethral fistulas, from whatever cause. Again let me emphasize that urethral fistulas do not follow the Cecil operation, and the best method of treating fistulas is to avoid them. They frequently occur after tunnelling operations, and flap operations if the flaps are under tension.

Fistulas that follow hypospadias operations may occur at any point. They may be of any size, from a minute fistula to a sloughing away of large portions of the urethra, but whatever size or wherever located, they are not easily cured by direct attack upon the fistulous tract, because the edges of these fistulas are often extremely thin and do not permit of the closures which are frequently depicted in the literature.

The one method which will certainly cure urethral fistula is one which I have previously described. It consists in denuding whatever urethra is remaining, bridging the defect, turning up lateral flaps, and burying the urethra in a midline incision in the scrotum, just as is done in the Cecil operation for hypospadias[11] (Fig. 21).

EPISPADIAS

This malformation occurs in both sexes. It is characterized by an absence of the roof of the urethra. In the male it may be balanotic, penile or complete. In the complete type there is total incontinence of urine. Epispadias is always present with exstrophy of the bladder, but may exist independently of exstrophy. In addition to a dorsal splitting of the urethra and rotation of the cavernous bodies outward, there is an associated ventral sagging of the foreskin. The glans penis is spatula-like. The floor of the urethra is represented by a moist, reddened channel. According to Campbell,[7] these patients, in later life, may have satisfactory erection and intercourse, but are usually sterile. In the female the degrees of epispadias may be clitoric, subsymphysial or complete. In marked degrees of epispadias in both sexes the pubic bones are widely separated, as are the recti muscles.

Surgery of Epispadias

The treatment of incomplete epispadias does not present serious surgical considerations, but the treatment of incontinence of urine associated with epispadias, in either sex, is uncertain in its outcome. In spite of this, one should not be dismayed should failure to bring about control occur even after one or two attempts to surgically cure it.

Boiffin, in 1895, described a procedure which is the basis for all operations for the cure of incontinence in epispadias. He stated:

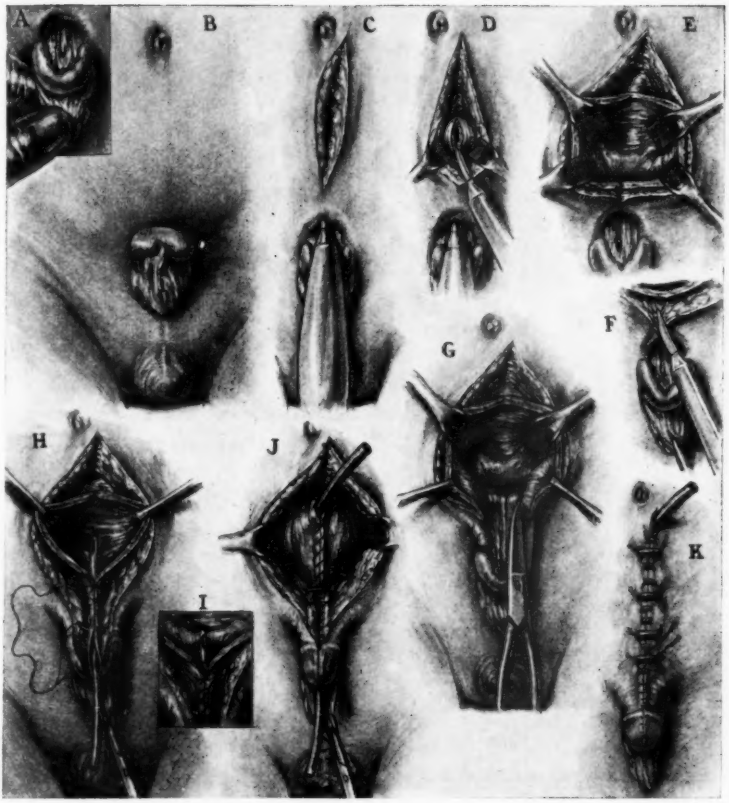

Fig. 22. Operation for epispadias in the male with incontinence, using division of the pubis, the technique regularly used by the author. *A*, The short spadelike penis is drawn down to show the widely open epispadiac urethra. *B*, Poor scrotal development and the usual appearance of the penis in these cases. *C*, With an instrument in the urethra as a guide, the bladder is opened. *D* and *E*, Exposure of the bladder floor. *F*, Division of the pubis and the urethral roof. *G*, The bladder musculature of the vesical outlet is trimmed away, leaving a strip of mucosa and underlying muscle about 3 mm. wide. *H*, The vesical neck and urethra are sutured with No. 1 chromic over a heavy nonabsorbable suture (to be left as a guide) rather than the silver probe here shown, as advocated by Young, from whose work these figures have been redrawn. *I*, In the closure of the vesical outlet it is highly important, and the most important step in the operation, that a large mass of muscle tissue be brought together at this point to insure subsequent control. *J*, Closure of the bladder and urethra with continuous fine chromic sutures; approximation of the pubis with silver or steel wire. *K*, External closure of the wound; cystostomy drainage with (not shown) a small temporary Penrose drain in the prevesical space. (Author's article in Campbell; Urology, Vol. III.)

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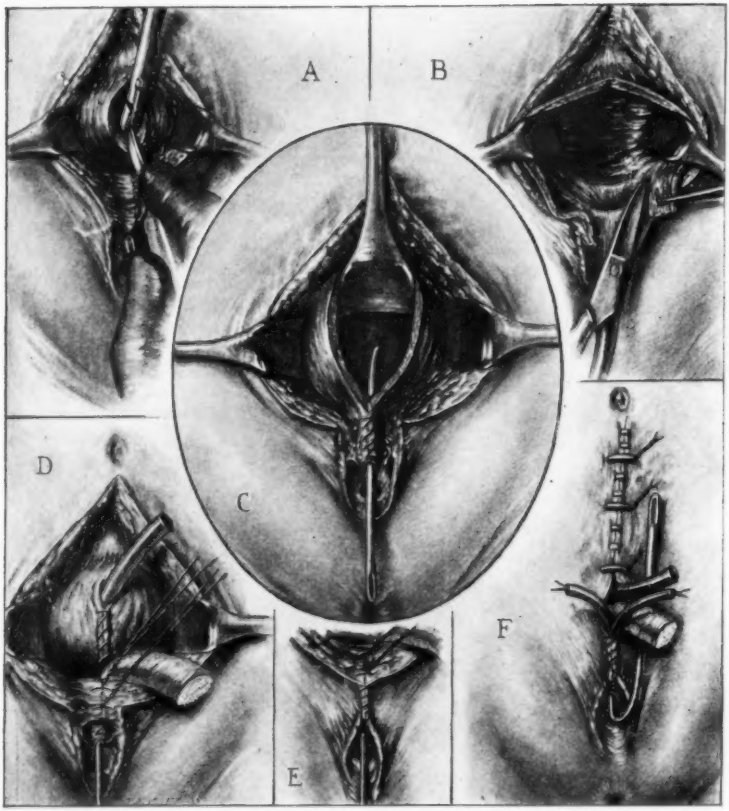

Fig. 23. Operation for epispadias in the female with incontinence. *A*, The pubis is divided; the bladder and the urethral roof are laid open. *B*, The bladder muscle at the vesical neck is widely trimmed away. *C*, The new urethra and the vesical neck are snugly sutured over a nonabsorbable suture which is brought out suprapubically above and from the urethra below as a subsequent guide if needed. In closing the bladder neck it is essential to include as large a mass of muscle tissue as locally obtainable. A drain is left in the space of Retzius for 2 or 3 days, and cystostomy drainage of the bladder is maintained for at least 2 weeks. *E*, Further details of the wound closure, with silver or steel wire to suture the pubis together. *F*, Skin closure with retention sutures; the cystostomy tube is in place in the bladder, a cigarette drain is in the space of Retzius. (Redrawn after Young.)

Incontinence of urine is due to a deep division of the circular fibers of the neck of the bladder. If the two ends of these fibers could be reunited, the functions of the neck of the bladder would be restored, particularly voluntary micturition. First I performed a symphyseotomy on the principles formulated by Farabeuf. Thus I exposed for the length of five centimeters the region of the neck of the bladder and of the prostate where the mucosa was present only along the median line. I dissected on the sides until I came to the thick fleshy parts, which I was able to suture with catgut and bring over to the median line over the mucosa, left intact at the bottom of the wound and

turned back like a fold on the side of the canal. Next, I sutured the symphysis with silk. . . .

Following Boiffin were articles by Trendelenburg, Young, Muschat, Sanchez-Cavisa and, more recently, Cecil, Dees and Campbell. Details of the operation for epispadias with incontinence, in both males and females, as carried out by Campbell, are shown in Figures 22 and 23.

I have found that, in rotating the cavernous bodies to bring them together, a great deal of tension on the sutures is brought about, and for this reason I suggest that through-and-through sutures, doubly locked, are superior to loop sutures. These sutures should be either dermal or fine metallic sutures. Figure 24 shows a perfect result which I obtained in a case of extreme epispadias which bordered on exstrophy in that one could see the bladder wall flapping into the opening. This patient has perfect control of urination, which he demonstrated before the Urological Section of the California Medical Association (1948). He is married and has normal sexual function.

Fig. 24. Cure of extreme degree of epispadias, with perfect urinary function. (Author's article in Campbell: Urology, Vol. III.)

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CRYPTORCHISM

Pathogenesis and Treatment

JOHN N. ROBINSON, M.D.

EARL T. ENGLE, PH.D.

It is tragic to contemplate that a child may grow to adult life harboring a potential cancer or not being able to have children because of lack of knowledge of or inadequacy in treating undescended testes. Treatment of cryptorchid testes is important to preserve fertility, to prevent traumatic damage and to avoid malignant transformation.

INCIDENCE

Testicles remaining undescended after puberty are few. There is a marked variation in the incidence reported by various authors.[4, 5, 7, 17] From 1 to 14 per cent are undescended at birth. The majority of these are descended by the time of puberty, leaving only one in 500 that has not descended when these boys reach maturity.

TYPES

A true cryptorchid testis by definition is one which stops or is halted in its normal course of descent from its embryologic position on either side of the second lumbar vertebra to the bottom of the scrotum. A maldescended testis is one that is stopped or stops in an abnormal position. They are found above the pubis, laterally, medially or anteriorly above the fascia after descending through the external ring. It

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is our intent to discuss only these types of undescended testes, unilateral or bilateral. Endocrine problems are not considered.

LOCAL EXAMINATION

The majority of cryptorchid testes are noticed on routine medical examinations; others are picked up later because the child has noticed he is not like other children; still others are picked up because the family has noticed a swelling in the inguinal region. Because it is difficult to be certain whether a testis is truly descended or not, we advise the following procedure: The child should be examined in an upright position if possible and should be steadied while the flat portion of either hand is placed firmly over the upper inguinal region and brought gradually downward, bringing the skin with it. Often the testis is felt under the lower edge of the hand as it slides downward. If in this position a testis cannot be felt, then the child should lie down on the examining table and a similar procedure followed. If a testis is still not found, the inguinal canal should be explored by palpation while keeping pressure on the inguinal region above. If these examinations fail to reveal a testis, the child should be placed in a tub of hot water and left there for about ten or 15 minutes in order to relax the cremasteric reflexes. When the testis can be palpated, it is important to determine its exact position and whether it is a true cryptorchid, or a maldescent, or whether it is the type which does not remain in the scrotum all the time.

EMBRYOLOGY

The gonad arises from the genital ridge on the posterior wall of the celomic cavity and extends from the sixth thoracic to the second sacral segment. By a process of growth and degeneration the testis reaches the abdominal end of the inguinal canal about the fourth to the seventh month. The testis passes through the inguinal canal in the latter part of the seventh month, but in many instances the final descent occurs in the early postnatal period.[15, 17]

To explain the descent or lack of descent is difficult; a number of factors have often been mentioned, but should be repeated. Most important are the following: anomalies of mesorchidium and gubernaculum, shortness of the cord, lack of scrotal development, small internal ring with large testes, congenital maldevelopment of testis, abnormal hormonal production.[15, 17]

PATHOLOGY

Studies by Charney,[3] Sniffin,[11] and the authors[10] have shown that there are approximately five stages in the normal development of the

testis: (1) prenatal, (2) static, (3) growth, and (4) maturity. Our studies have shown that at the age of four or possibly five there is little difference between the testes of normally descended and cryptorchid.

As the child grows, however, these undescended testes will not grow as rapidly in size, nor will they catch up to the normal mate either in

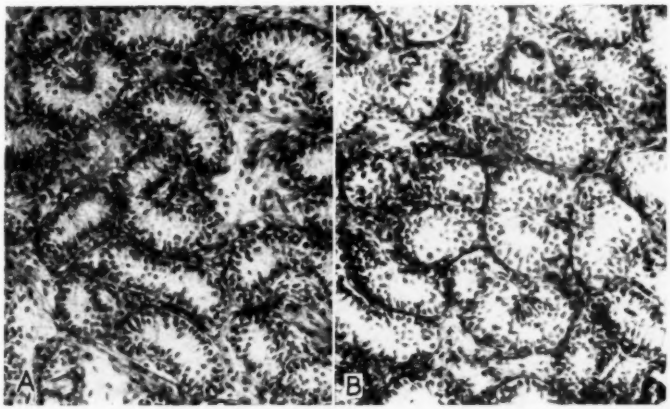

Fig. 25. Photomicrographs, high power view, of (*A*) a cryptorchid testis and (*B*) a normal testis, biopsied at the same time at operation on a 5 year old boy. Note the similarity of the sections.

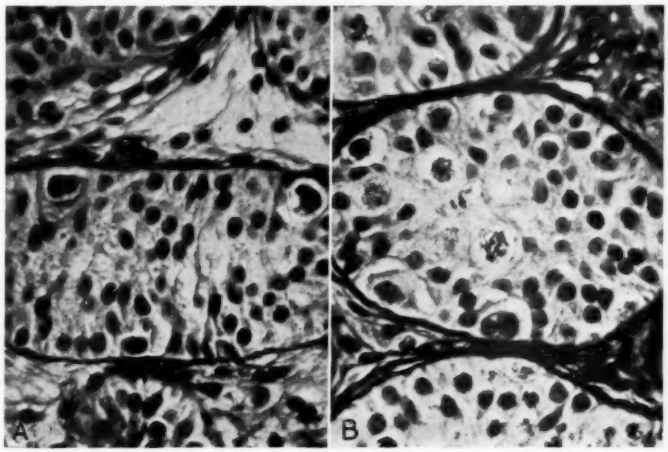

Fig. 26. Photomicrographs, high power view, of (*A*) a cryptorchid testis and (*B*) a normal testis biopsied at the same time at operation on a 9½ year old boy. Note the differences in the sections.

spermatozoa production or in size of the tubules, as seen in Figures 25 and 26.

These studies apply only to the size and to the fertility pattern of the undescended testis as compared to the normal. Sohval[3] states that the incompletely descended gonads of 42 patients were studied to elucidate the relationship between the maldevelopment and the maldescent of the testis. Special attention was devoted to the detection of histologic evidence of the defective gonadogenesis. Three varieties of testicular dysgenesis were encountered. The most frequent type was seminiferous tubular immaturity occurring at or after the prepuberal age. This was noted in approximately half of the cases. Much less frequent was another type of congenital lesion characterized by complete absence of spermatogonia (germinal aplasia) just before and during the puberal period. The least frequent and most profound developmental defect was found in the rudimentary testis of a hypergonadal adult. In this instance germinal, Sertoli and Leydig cells were absent.

Sohval states that the high incidence of dysgenic testicular lesions in this series of undescended testes supports the view that testicular imperfection is of etiologic significance in some cases of cryptorchism. We are not in agreement that the seminiferous tubular immaturity which he described is a noncorrectable congenital lesion, but like to think this is due to failure of the tubules to develop, probably because of thermogenic factors resulting from poor position. It cannot be doubted that Sohval's other cases of germinal aplasia and rudimentary testis are of congenital origin and may well be responsible for this type of testis not descending or in development of cancer.

Another factor in the pathology of the undescended testis, which disturbs us, are reports of three biopsies taken at the time the second stage of a Torek operation was performed. The testis had been attached to the thigh. Is damage to this cryptorchid testis due to operative intervention or is it congenital?

Another factor which must be considered in the treatment of the cryptorchid testis is the fact that in our series of 30 testes biopsied for fertility ten years after previous operation at puberty, only two testes were completely normal.

In review, the undescended testis does not develop equally with its normal counterpart after the age of four or five. Approximately 50 per cent of undescended testes which do not develop are or may be congenitally defective.[7] Biopsies done at the time of a second-stage Torek operation and after a previous orchidopexy show many damaged testes as far as fertility is concerned, though their size may remain the same and the interstitial cells are normal.

TREATMENT

Aims of Treatment

The aims of treatment are (1) to prevent development of cancer, (2) to obtain the maximum fertility, (3) to prevent damage by trauma to the testis because of its abnormal position, and (4) to obtain a normal cosmetic result. These aims can best be met by placing the testis in the normal scrotal position at the earliest possible time.

Indications for Operation

If a child with a unilateral or bilateral undescended testis is not treated until puberty or later, the incidence of torsion is increased because of the loose attachment of the epididymis and testis; the danger of trauma is more marked in those testes being exposed in the inguinal canal; the incidence of cancer may become greater with each year.[2] Strangulation of the associated hernia is more likely to occur, and finally fertility may be irrevocably lost.

On the other hand, if testes are left untreated and do come down during or after puberty, we have no assurance that they have reached normal maturity or whether they are congenitally defective or are more likely to develop cancer than the normally descended one and slightly less likely than the early replaced testis.

Methods of Treatment

There are many methods of treating the cryptorchid testis. First of all there is the conservative treatment whereby the family do not wish any operation and believe that the testis will come down by itself. The reasons for not waiting have been considered. Various other non-operative methods and operation are considered. Any testis which is not a true cryptorchid testis, or has a hernia, should be corrected as soon as noted and proved. In the years since one[6] of us first described the descent of the testes in the immature Rhesus monkey, gonadotropins or similar substances have been injected frequently over a long period of time. These substances produce a certain number of descents in those testes that will come down without treatment, but when, on the other hand, they are given over a long period of time, they cause early sexual maturity, chronic prostatitis, and enlargement of the genitals to a stage of embarrassment. Antuitrin S is still recommended in doses of 250 units two or three times weekly for three to four weeks. If good results are not obtained, it should be discontinued.

The Diagnostic Test

We have been using a more concentrated product, A.P.L., Brand of Gonadotropin made by Ayerst, McKenna and Harrison with 10 cc. containing 20,000 units. We believe that the child should have 4000 units daily for three days for a total dosage of 12,000 units. If within one week or ten days the testis has not descended, then we believe that an exploratory operation should be performed. In other words, we use injection not necessarily as a method of causing the testis to descend, but rather as a diagnostic procedure which shows us which testes have mechanical obstruction and which ones would probably come down by themselves and have no real obstruction. We have already treated over 20 cases with these injections. In only two cases did the hormone fail to give us the desired information. In other words, in these 20 cases the testis descended in only two, but in all the others, except when the testis was intra-abdominal, the hormones failed to cause testicular descent, leading us to make the diagnosis of mechanical obstruction, which was proved at operation. The abdominal testes which we have mentioned probably failed to descend because of extremely short structures.

In our hands this has been a valuable procedure. The advantages of this form of injection are that only three injections are required. The child has to stand this procedure for only a short time. There are no sexual changes involved. The injection is easy to administer, and also we feel that it gives a fairly reliable diagnostic test as to whether one should operate at an early age or possibly wait for a short time or longer. Injections can be repeated whenever necessary within reason.

Time of Operation

In view of the pathology which we[10] and others[3, 11] have reported, and the poor development of previously operated testes, and recent reports[12] that results cosmetically were just as good in the group under three as in the group between ten and 12, we strongly advise operation before five years of age. Earlier operation may be advisable if other pathology such as hernia exists.

Operation

The operation for cryptorchid testes was described by Arthur B. Bevan in 1899 and in 1903.[1] His latter description is so explicit that little improvement has been made in the concept of operation. Others,[8, 9, 10, 15, 17] including Bevan,[1] have made modifications in the operation in order to prevent retraction of the testicle. In this paper we are

not primarily concerned with the technique of operation, and we shall only mention certain points. A high transverse incision may be used instead of the normal oblique inguinal one with less likelihood of keloid formation. It is important to mobilize the spermatic cord and testes completely, using all the modifications to obtain the necessary length and to keep the testes in the scrotum. *If the testis after a normal mobilizing procedure will not reach the scrotum easily, then it is necessary to use all the modifications previously described,* such as freeing the vessels retroperitoneally, placing them under the epigastric vessels, using various methods of fixing the testis to the scrotum and thigh. However, each case is an individual problem, and the final decision must be left to the surgeon.

Fate of the Inadequate Testis

There are several decisions to be made at the time of operation: If the testicle can be brought into the scrotum with moderate or heavy tension, it is necessary to use a Torek type of procedure, suturing the testis to the thigh. If mild tension is necessary, the elastic traction may suffice. If the testicle cannot be brought to the scrotum, but reaches the pubic bone, it is necessary to consider (1) removal, (2) leaving the testicle in the groin with the idea of a second operation at a later date. At present, if the testis is small and of the congenital type, we recommend removal. If the testis is normal, we prefer to leave it in the groin for a definite time and then attempt a second operation with the hope that it can be placed in the scrotum. If not, it should be removed. If the testis has such short structures that it cannot be pulled out from the abdomen, and the other testis is normal, it should be removed. If both testes are intra-abdominal, it is probable that both could be removed and the patient carried on replacement therapy, though at this time we are not ready to recommend such a radical procedure.

It has been our experience that the function of many small testicles seen at operation cannot be adequately determined. A frozen section is inadequate, and we are now searching for a new quick test to find out which of these testes have germinal aplasia or are rudimentary and will never develop or which ones have possibilities of developing normally. When we are certain, we recommend removal at the time of the original operation when possible. The question arises whether these congenital types of testis are more apt to form cancer. At present, information is not at hand which will give us the answer. If the child shows any signs of a psychic reaction because of the loss of one or two testicles, we now have extremely suitable plastic testes which can be placed in the scrotum.

SUMMARY

A short discussion covering undescended testicles from the first examination to the final result has been presented. To us it seems that the undescended testis should be replaced before the age of five unless there are other, more important considerations. If there is no response to gonadotropin substances, then operation is recommended.

If we can persuade you to do biopsies or recommend that they be taken on all cases of undescended testicles at the time of operation, if we can persuade you to do your operations early, and if a careful follow-up study can be arranged, we hope that definite answers to the questions of which undescended testes develop cancer and which ones remain sterile can be settled. Until then we recommend that all undescended testes should be replaced early.

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UPPER URINARY TRACT OBSTRUCTIONS IN INFANTS AND CHILDREN

Diagnosis and Treatment

HUGH J. JEWETT, M.D.

Obstructions confined to the upper urinary tract are more often unilateral than bilateral. In either case they may be multiple, and in bilateral obstructions the dilatation of one upper tract usually exceeds that of the other. The degree of obstruction varies from minimal to complete. When it is sufficient to cause a significantly sustained increase in hydrostatic pressure, the end result is hydronephrotic atrophy. When unilateral, this atrophy may progress silently to completion. When it is bilateral, impairment of total renal function occurs, but this, unless searched for, may escape notice until it is advanced. Preservation of the kidney requires corrective intervention before the damage has become irreparable.

In any given case the rapidity with which hydronephrosis develops depends primarily on the degree of hydrostatic pressure sustained more or less continuously by the kidney. Forces concerned in the maintenance of such increased pressure are the rate of accumulation of urine within the renal pelvis versus the rate of its removal, which is governed principally by the degree of obstruction, and to a less extent by the amount of reabsorption. Secondary factors which increase the speed of hydronephrotic atrophy are the proximity of the obstruction to the kidney, an intrarenal pelvis, and enough vascular insufficiency to impair parenchymal nutrition in some areas without abolishing glomerular filtration in others.

Urine discharged from the collecting tubules into the minor calyces does not trickle continuously down the normal ureter into the bladder. It is ejected in spurts from the minor calyces, and thence is propelled

by a system of segmentally arranged peristaltic contractions. The rate and amplitude of these waves of contraction vary at different levels, but those at the lower end of the ureter are strongest and force the urine through the ureteral orifice in intermittent jets. The renal pelvis in children ordinarily empties completely in five minutes, and retention longer than this after retrograde injection of contrast solution indicates stasis. Peristaltic activity is enhanced by, but not entirely dependent on, the extrinsic nerve supply, which is believed to be sympathetic except at the lower end of the ureter. Here the reflection of a layer of musculature derived from the bladder (Waldeyer's sheath) provides increased muscular strength, and in this area cell bodies of postganglionic parasympathetic motor fibers can be found, as in the bladder wall.

Fig. 27. Hydroureteronephrosis from ureteral stricture. Secondary obstructions from angulations and looping. (Jewett: Surg., Gynec. & Obst., Vol. 68.)

Many authors have stated that there are three points of physiologic narrowing of the ureter in the male—the ureteropelvic juncture, the uretero-iliac crossing, and the ureterovesical juncture. In the female, contact with the uterine artery in the broad ligament region has been illustrated as a fourth narrowing. In many cases, however, after the ureter has been removed from the body these "normal narrowings" seem to disappear except at the lower end, and occasionally at the upper end also, in which case it is often difficult to exclude an intrinsic obstruction of minimal degree. Of 50 upper urinary tracts removed from stillborn infants at routine autopsy, only eight had a demonstrable ureteropelvic juncture. In 42 cases the funneling was so gradual that it was impossible to tell where the

pelvis ended and the ureter began.[5] This observation was in marked contrast to that of Felix,[2] who found the upper end of the ureter to be narrow in all embryos whose length exceeded 125 mm.

In children most obstructions are congenital in origin and partial in degree. According to Campbell,[1] 10 to 14 per cent of infants are born with some anomaly of the urinary or genital tract. Urologic disease in infants and children, resulting principally from some malformation, consists in obstructions and infections in 90 per cent of the cases.

When the bladder and lower urinary tract are normal, residual vesical urine is absent and reflux of urine into the ureters ordinarily does not occur. In most cases, dilatation confined to the upper urinary tract is the result of back pressure from a localized mechanical obstruction. This pressure varies directly with the degree of obstruction. If the latter is partial, and the pressure increased only slightly, the musculature of the tract above compensates by undergoing work hypertrophy, characterized by a general muscular thickening. If the obstruction is marked and the pressure high, rapid decompensation, atony and dilatation occur. This dilatation usually commences just above the site of obstruction and progresses gradually upward, so that the farther the obstruction is from the kidney, the longer the latter is protected by the intervening tract. In the case of low ureteral obstructions the ureter may absorb moderate pressure for a considerable time. But if the pressure is high, the ureter rapidly undergoes progressive dilatation, elongation, angulation and looping which may cause secondary obstruction (Fig. 27). Hydroureteronephrosis thus produced usually is unilateral, but may be bilateral and asymmetrical. Its development is accelerated and made less reversible by infection, which frequently supervenes.

MECHANICAL OBSTRUCTION

The principal causes of mechanical obstruction of the upper urinary tract fall into three groups, depending on the position of the obstructive factor with relation to the ureteral wall: the extramural, the intramural, and the intraluminal.

Extramural conditions, obstructing the ureter by pressure against it, are large fecal impactions, intraperitoneal abscess, tumor, blood vessels (aberrant; postcaval ureter), isthmus of a horseshoe kidney and other renal anomalies, hypertrophy of the bladder musculature, vesical diverticulum, ureteral diverticulum, and fibrous bands principally at the upper end.

Other external conditions resulting in ureteral obstruction are angulations or kinks with fixation usually associated with vessels or fibrous bands, congenital torsion or spiral twists, and periureteral fibrosis, which

generally follows retroperitoneal inflammation or hemorrhage about the ureter.

Intramural conditions, or intrinsic narrowings of the ureteral wall itself, are usually organic, although dynamic factors are said to be

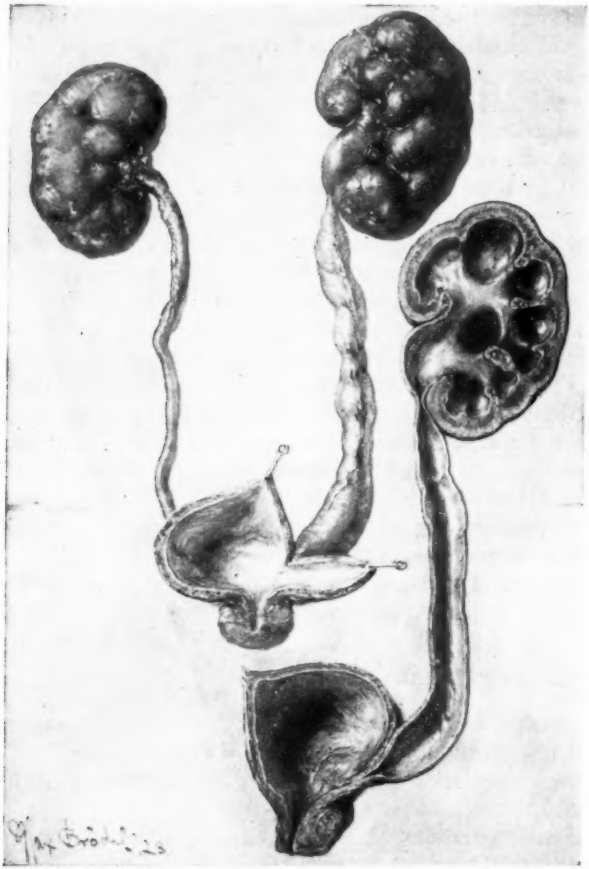

Fig. 28. Autopsy case. Newborn male infant showing unilateral hydroureteronephrosis from congenital stricture of intramural portion of ureter. (Young and Davis: Young's Practice of Urology.)

responsible at times. Among the organic conditions which may be encountered are stenosis of the ureterovesical orifice, with or without ureterocele or ectopy, congenital stenosis of the intramural or juxtavesical ureter (Fig. 28) or of the ureteropelvic juncture, hypoplastic ureter at either end, and edema from acute inflammation.

Dynamic obstruction produced by spasm of the ureteropelvic juncture

has been reported to cause hydronephrosis in the exceptionally rare case.

Intraluminal obstruction usually is caused by a stone. Rarely it may result temporarily from a blood clot and very rarely from a polyp, mucosal fold or ureteral valve. The valve may appear as a leaflet of mucosa or even as an iris type of diaphragm across the entire ureteral lumen (Fig. 29). External inspection discloses no narrowing, and its identification requires ureterotomy.

Obstruction at the upper end of the ureter, the so-called ureteropelvic juncture, causes larger and more rapid hydronephrosis, and the ureter below usually is normal. Of 71 cases operated upon at the Brady Urological Institute for noncalculous, nontuberculous obstruction at this level, the underlying cause was congenital stenosis in 60 per cent (Fig. 30), accessory renal vessels in 34 per cent (Fig. 31), and kinks with fibrous bands and fixation in 6 per cent.[5] Spur formation resulting from a high insertion of the ureter into a redundant renal pelvis is a frequent cause of obstruction, but is usually, if not always, secondary to a primary stenosis, aberrant vessel or kink with fibrous band and fixation.

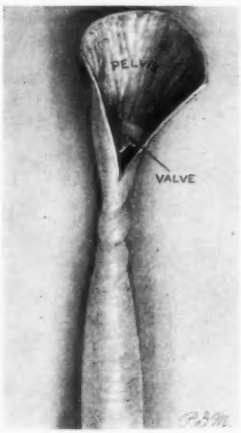

Fig. 29. Autopsy case. Newborn infant showing an iris type of diaphragm across the ureteropelvic junction. (Everett: Obstetrical and Gynecological Urology. Baltimore, Williams & Wilkins Company.)

Of the 43 cases with primary congenital stenosis, ten were associated with accessory vessels which were factors of only secondary importance in the obstructive process (Fig. 32). In 24 cases, obstruction was caused by the vessels alone.

When stenosis was the primary cause, secondary accelerating factors often were accessory vessels, infection, kink with band and fixation, and high ureteral insertion. When vessels were the only demonstrable cause, with cure following simple division and ligation, the obstructive contact was believed to have been established by the normal growth of the kidney. During this growth the poles diverge, the long axis becomes nearly straight, and the infantile intrarenal pelvis may be extruded against an aberrant vessel attached to the lower pole.[4] Nephroptosis and malrotation also may be factors producing obstructive contact in some cases.

Vesico-ureteral Reflux of Urine

Reflux of urine from the bladder into one or both ureters occurs when the intramural course of the ureter has become sufficiently altered

to impair its normal valvelike function. The accumulation of urine, forced into the ureter from the bladder, increases the hydrostatic pressure within the ureter and causes it to undergo progressive dilatation, elongation, angulation and looping (Fig. 33). If infection is present, the dilatation may be accelerated and made less reversible because of disorganization of the ureteral musculature.

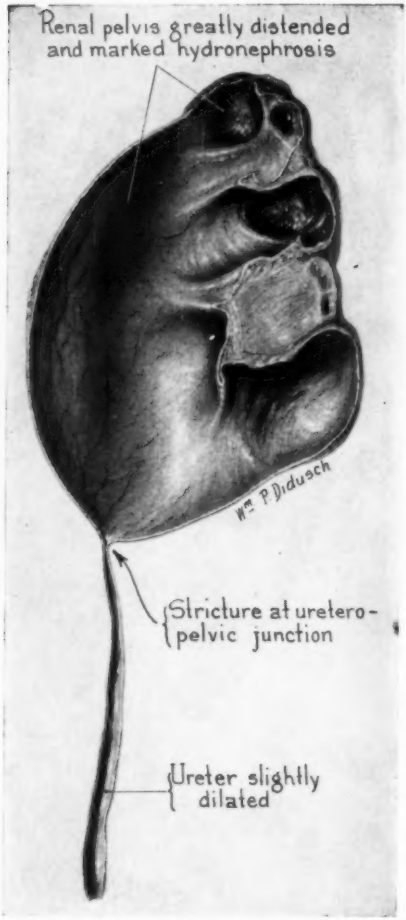
Renal pelvis greatly distended and marked hydronephrosis
Wm P Didusch
Stricture at ureteropelvic junction
Ureter slightly dilated

Fig. 30. Sectional view, right hydronephrosis caused by congenital stenosis at ureteropelvic junction. (Jewett, in Cecil, R. L., ed.: Specialties in General Practice.)

Vesico-ureteral reflux nearly always indicates previous damage to the bladder from (1) infravesical obstruction causing increased intravesical pressure, (2) neuromuscular disease, or (3) both, and is usually bilateral. When the damage is marked, the ureteral orifice is large, rounded and gaping, and the ureter passes straight through the bladder wall instead of obliquely. Occasionally the underlying vesical damage and its cause are sufficiently slight to escape detection on casual study. In fact, even vesico-ureteral reflux as the cause of hydroureter may be overlooked unless it is thought of and excluded by careful search. At times it is demonstrable only in the voiding cystogram, and Stewart[10] has shown that in some cases it can be recognized only by making delayed cystograms. In this procedure the bladder is kept full of contrast solution for an hour or more and roentgenograms are made at regular intervals. In cases in which the reflux is so difficult to establish the ureteral orifice looks normal on cystoscopy, instead of rounded and patulous, and the direction of the intramural ureter deviates only slightly from its usually oblique course, with or without a coexistent ureteral stricture.

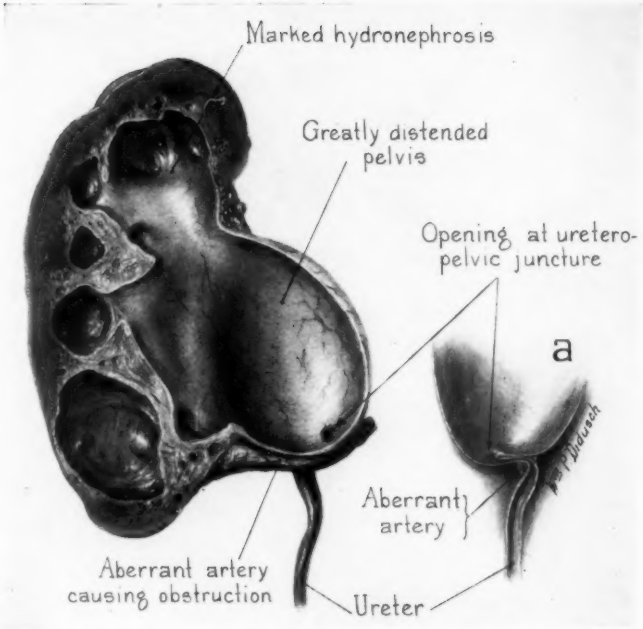

Fig. 31. Hydronephrosis caused by aberrant artery just below the ureteropelvic junction. No stenosis. (Didusch: Collection of Urogenital Drawings. New York, American Cystoscope Makers, Inc., 1952.)

NONMECHANICAL OBSTRUCTION

Adynamic conditions localized to the ureter are still poorly understood, but into this group some authors place all cases of hydroureteronephrosis in which they are unable to demonstrate a mechanical cause of obstruction after careful cystoscopic search. Caulk in 1923 was the first to apply the term "megaloureter" to this condition. True primary megaloureter, however, is rare, and nearly all cases of dilated ureter can be explained on the basis of mechanical obstruction, infection or vesico-ureteral reflux of urine.

The fact that an undilated segment of the ureter can accommodate a catheter of fairly large size or even a bulb bougie does not necessarily rule out a congenital stenosis any more at the lower end than at the upper. In many cases of congenital obstruction of moderate degree at the ureteropelvic juncture the stenosis will accept an instrument forcibly introduced, and yet will impede the free passage of urine propelled by relatively feeble peristaltic pressure. After the completion of renal ascent in the rapidly growing embryo, the two ends of the ureter, representing

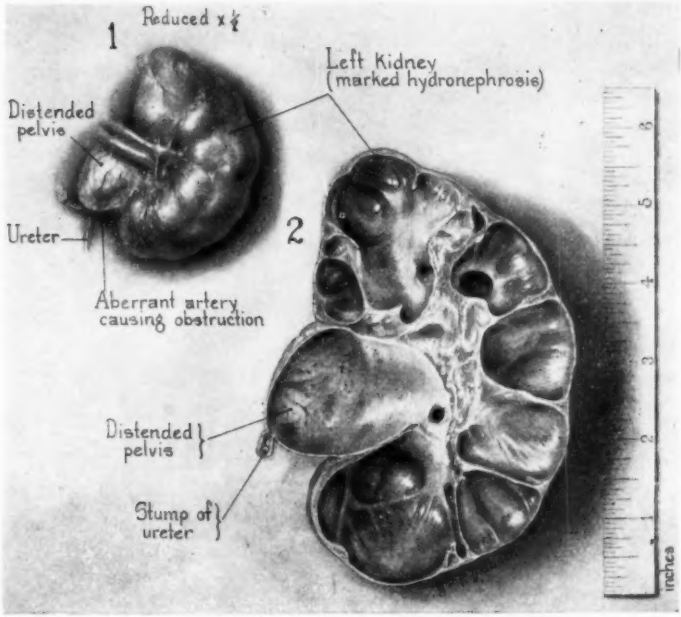

Fig. 32. Congenital stenosis of ureteropelvic junction associated with accessory renal vessel. Complete hydronephrotic atrophy. (Jewett: J. Urol., Vol. 44.)

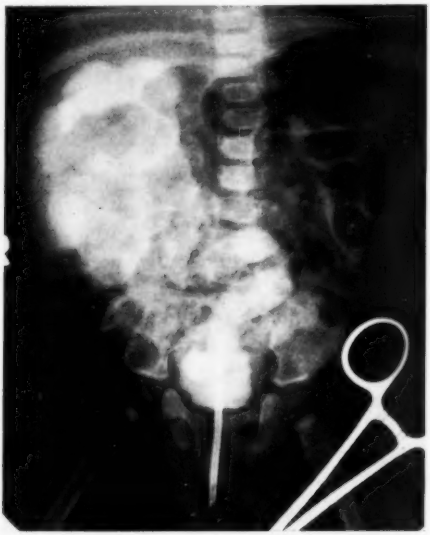

Fig. 33. Cystogram showing marked hydroureteronephrosis, right, from reflux. Marked elongation, angulation and looping of ureter.

more or less fixed points, are prone to become the sites of congenital stenosis of varying degree.

Chronic infection of the ureteral wall and of the renal pelvis may produce sufficient disorganization of the musculature to reduce or even abolish effective peristaltic activity, and lead to moderate dilatation and atony. If this complication should be superimposed upon a ureter already having difficulty compensating for a moderate obstruction, decompensation and the development of hydroureteronephrosis will be rapidly accelerated.

The term "primary megaloureter" should not be applied when vesicoureteral reflux of urine can be demonstrated, for obviously the primary condition is elsewhere. Swenson and his associates[11] have attributed megaloureter in some cases to a deficiency or absence of cell bodies of postganglionic parasympathetic motor nerves which normally are concentrated in the adventitia of the bladder near the entrance of the ureter. When such a deficit results in hydroureter, however, the condition obviously is secondary to a congenital neuromuscular disturbance of the bladder wall, and most of Swenson's patients had free reflux of urine from the bladder.

In an attempt to draw an analogy between the primary megaloureter with an undilated lower segment and Hirschsprung's disease, Swenson and his co-workers studied some of these ureters for nerve cells. They found, however, only occasional ganglion cells in normal ureters and in megaloureters, and state that their investigations permitted no conclusions. Lewis and Kimbrough[7] also examined histologically a number of undilated lower ureteral segments in cases of suspected primary megaloureter and were unable to demonstrate absence of nerves by silver stains. Nevertheless there is some evidence that in the exceptional case there may be some primary neuromuscular disturbance confined to the lower, undilated ureteral segment. Nesbit and Withycombe[9] reported three cases in which stimulation of the dilated upper ureteral segment caused peristalsis which terminated in the undilated segment 2 to 4 cm. from the ureterovesical junction. Milton and Robb,[8] furthermore, found electrical activity to be present in the dilated segment, but to be not appreciably demonstrable in the undilated portion.

Dilated ureters associated with congenital absence or deficiency of the abdominal musculature have been attributed to an alleged arrest of the muscular development of the ureter. From the embryologic standpoint, however, the suggestion is not convincing. The abdominal musculature, derived from the myotomes, is normally present, although not fully developed, in a 20-mm. embryo.[6] The ureteral musculature is laid down much later, and is not developed from the myotomes. In 1939 the late Dr. George L. Streeter, Director of the Department of Embryology, Carnegie Institution of Washington, and I examined serial sec-

tions of numerous human embryos. Bladder muscle and Waldeyer's sheath were well developed in the 81-mm. embryo, but the ureteral musculature was not present (No. 2093). In the 100.5-mm. embryo primitive muscle was present in the pelvic portion of the ureter and at its upper end, but was completely absent in the middle ureter (No. 1908). It was not until the embryo had attained a crown-rump length of 126 mm. that muscle could be seen enveloping the ureter through its entire length. At this stage the ureters were large and bulged into the celomic cavity (No. 1358G).

In summary, then, the overwhelming majority of cases of hydroureter are caused by mechanical obstruction or vesico-ureteral reflux, with or without infection, and each at times may be difficult to demonstrate. Primary megaloureter is extremely rare, but there is evidence in some cases that the lowet undilated segment lacks normal peristaltic activity even though histologic studies show the presence of some nerve cells. Up to now there is no conclusive evidence that primary megaloureter results from an absence of postganglionic parasympathetic motor nerves in the ureteral wall itself.

SYMPTOMS

When obstruction is confined to one upper urinary tract and uncomplicated by infection, hydronephrotic atrophy may progress to completion without producing symptoms, especially in infants. Occasionally in older children discomfort is entirely absent, but pain may vary from a slight abdominal ache or occasional twinge in the flank to severe renal colic with radiation to groin, testis, labium or leg. The colic usually is the result of spasm of the musculature of the renal pelvis or ureter. Between these extremes there may be gastrointestinal disturbances such as anorexia, nausea, vomiting, flatulence, indigestion or constipation, often from pressure on the viscera. Hematuria occurs now and then, and may be profuse if the dilated kidney sustains only minimal trauma. Incontinence in females, persisting since birth and especially noticeable after the age of four years, sometimes results from an ectopic ureteral orifice. The involved ureter usually is dilated and often drains one pole of a double kidney.

When the obstruction is bilateral, or the opposite kidney is functionless, loss of appetite, nutritional disturbances resulting in failure of the child to gain weight and develop properly, polyuria, occasionally polydipsia and even frank uremia may appear. With adequate fluid intake urinary output is not reduced unless the obstruction is nearly complete and bilateral, or unilateral with a functionless renal mate.

The occurrence of infection which sooner or later supervenes eventually complicates the picture in both unilateral and bilateral obstructions.

Fever, however, may be the only symptom, and a red throat or eardrum may seem sufficient to explain it. Subsidence of fever with chemotherapy does not protect against the ravages of obstruction, and urinalysis is always indicated when fever is persistent, recurrent or not obviously explained.

In addition to the symptoms mentioned, chills and toxemia often are present. If the obstruction is incomplete, so that the infected urine can reach the bladder, vesical irritability, consisting in urgency, frequency, precipitate urination, nocturnal enuresis, and pain and burning on urination, is not uncommon. Persistent infection in either sex may result from an infected hydronephrotic segment of a double kidney, with or without an ectopic ureteral orifice.

DIAGNOSIS

Occasionally a large hydronephrotic sac can be seen as a smooth, rounded mass bulging into the flank or abdomen, and perhaps displacing the colon or stomach. When the enlargement is less marked, tenderness sometimes can be elicited by palpation or gentle percussion in the costovertebral angle, or by deep bimanual palpation in the renal area. When the kidney is palpable, it usually moves with respiration; if the cystic mass is tense, it may be indistinguishable from a solid tumor. The absence of palpable masses, however, does not exclude hydronephrosis.

The urine is more often abnormal than normal. Albuminuria and pyuria are fairly common, and erythrocytes are not infrequently found in the centrifuged sediment. In cases of bilateral obstruction with diminished total renal function the specific gravity will be low. If pyuria persists two to three weeks, or recurs after chemotherapeutic sterilization, roentgenograms are a necessity. Rectal examination will exclude a pelvic mass pressing on the urinary tract, and may disclose dilated ureters and loss of anal sphincter tone. The latter suggests neuromuscular disease of the bladder.

The presence of obstruction and its localization, the extent of the damage sustained by the tract above, the condition of the opposite kidney and the selection of the most appropriate method of treatment will depend on urography (Fig. 34). Excretory urograms at times furnish sufficient information, but in many cases cystograms, cystoscopy and retrograde pyeloureterograms become necessary.

In order to rule out a lower urinary tract obstruction and vesicoureteral reflux, it is necessary to pass a small, sterile soft rubber catheter. This will disclose the patency of the anterior urethra and the presence or absence of residual vesical urine. The catheter naturally should be

passed immediately after the patient has voided, and if necessary may be left in place until the phenolsulfonphthalein test is made.

When the child's general condition has been improved as much as possible, acute infection fairly well controlled, and constipation relieved, he should be prepared for light ether anesthesia for cystography and cystoscopy. The cystogram, made in order to exclude vesico-ureteral reflux, is obtained by filling the bladder by gravity with 10 per cent

Fig. 34. Excretory urogram showing partial congenital stenosis at lower end of each ureter with dilated ureter above obstruction.

Skiodan through a soft rubber catheter. Delayed cystograms have already been mentioned as a useful method of establishing such reflux in the elusive case,[10] but this procedure can be postponed until it becomes evident that mechanical obstruction to the upper urinary tract does not exist.

The urethra is then calibrated with children's sounds having a short curve, and gently dilated up to a number 14 French size if possible, since a number 14 French infant cystoscope accommodates two number 4 French ureteral catheters. A number 11 French cystoscope may be used for simple observation of the bladder and urethra. Failure to find a ureteral orifice may be overcome by injecting indigo carmine intravenously, provided the kidney is functioning. In infants an average dose is 0.5 cc. of a 0.4 per cent solution; in older children, 1 cc. for every two years of age up to 5 cc. Differential renal function in the very young is determined better by chromocystoscopy than by the collection of phenosulfonphthalein from each of two indwelling ureteral catheters, because

their small lumens prevent adequate drainage. An accurate test depends on proper hydration, which demands intravenous fluids when the patient is under general anesthesia. The indigo carmine then can be injected through the rubber tubing just above the needle. After the catheter has been passed into a dilated renal pelvis a fast flow or stream of dilute urine may escape from its outer end. In obtaining the retrograde pyelogram care must be taken not to overdistend and rupture the renal pelvis. When there is no clue to the size of the pelvis, it is safer to inject no more than 0.3 cc. of 20 per cent Skiodan if the infant is under three months of age, increasing only slightly for every three months up to two or three years of age. The film then taken will show whether more solution should be injected to make a final diagnosis.

Delayed pyeloureterograms often are helpful in indicating stasis or retention. The renal pelvis in children ordinarily empties completely in five minutes or less. Retention of contrast solution longer than five minutes after retrograde filling of the renal pelvis is evidence of obstruction.

These delayed films often are of the greatest importance in determining the existence of primary and secondary mechanical obstructions. Angulation and looping of the ureter may or may not result in secondary obstructions. If, however, contrast solution deposited in the renal pelvis is retained five or ten minutes in the tract above such kinks while the lower ureter and bladder remain empty, the kinks are obstructing. If, on the other hand, the solution drains down promptly to the lower end of the ureter, but not into the bladder, the hydroureter almost certainly is caused by a primary low ureteral obstruction.

TREATMENT

The immediate surgical objective is the release of hydrostatic pressure, so that renal function may be preserved or restored, and infection controlled. In some instances this objective may be reached by cystoscopic manipulation; in others, by conservative surgery. If, however, the damage is irreparable and limited to one side, nephrectomy generally is indicated if the other kidney has normal function. The choice of procedure naturally depends on definitive diagnosis.

It is almost axiomatic in urology that the closer the surgical drainage is to the kidney, the more efficient it is. This principle applies particularly to cases of mechanical obstruction from ureteral angulation and looping secondary to either a primary low ureteral obstruction or vesico-ureteral reflux. Apparent upper ureteral kinking, however, is not always obstructive, and one hesitates to undertake nephrostomy if a single procedure, for elimination of the primary factor, will suffice.

Mechanical obstructions involving the lower end of the ureter may

respond to conservative management, which includes cystoscopic treatment. Small, delicate ureteroceles, stenotic ureteral orifices and short strictures of the intramural portion of the ureter (within the bladder wall) may be eliminated by cystoscopic electro-excision and fulguration, meatotomy and dilatation. The latter can be carried out periodically, but unless the child is large enough to permit the use of instruments of adequate size, it usually is better to open the bladder and carry out prompt and definitive treatment. In the case of stenosis

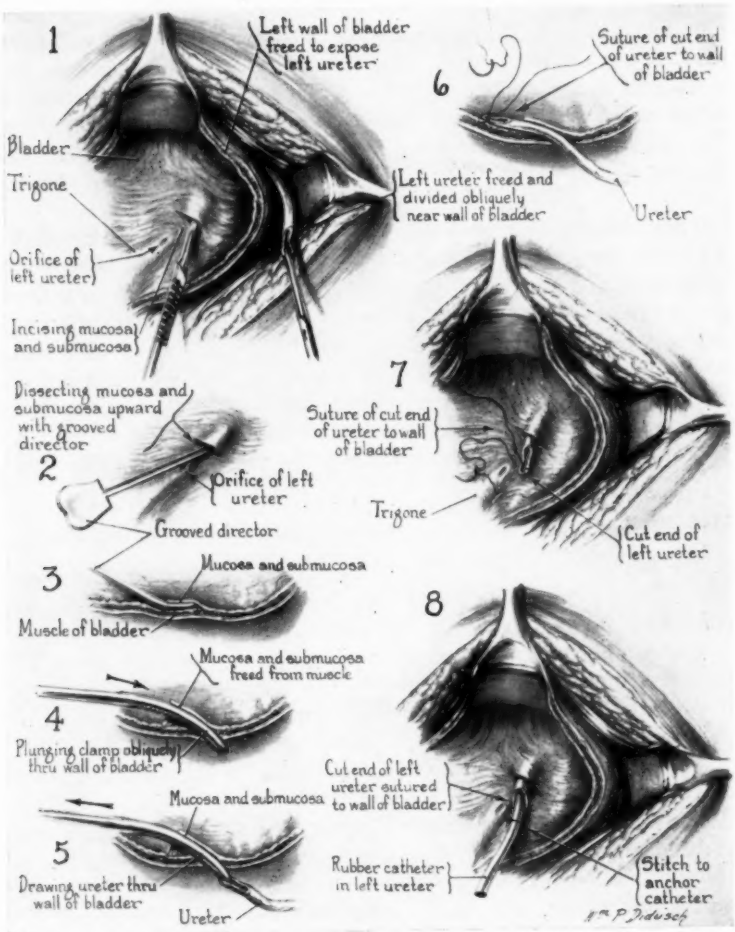

Fig. 35. Author's method of reimplantation of ureter into bladder. Direction of implanted ureter is oblique and submucosal.

of the ureter within the bladder wall or just external to it a wide meatotomy through the opened bladder is safer and more effective, and the ureter can be intubated with a fairly large catheter for a week or so to prevent contraction of the incised edges.

Obstructions of the upper ureter, except those temporarily caused by a small calculus, nearly always require open operation. Most of these obstructions involve the ureteropelvic juncture, and the type of operation will depend on the pathologic condition that is found. Stenoses

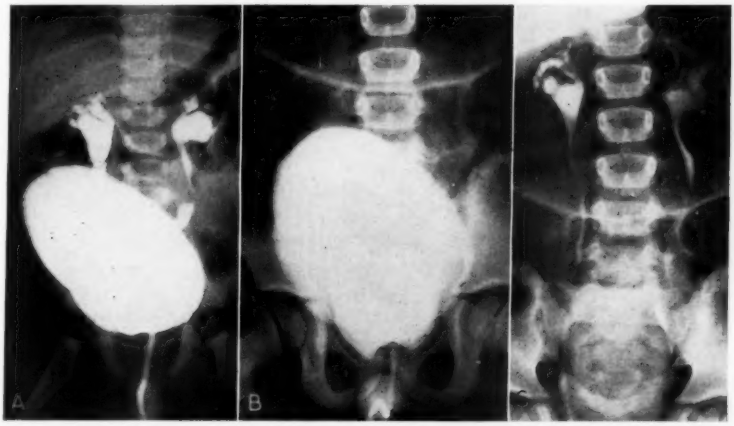

Fig. 36. A, Cystogram showing large bladder with reflux of solution into both ureters, resulting in complete bilateral pyelogram. Underlying cause is neurogenic bladder with atony. Relative obstruction at bladder neck also present. Marked renal damage. (Jewett, in Cecil, R. L., ed.: Specialties in General Practice.) *B*, Postoperative cystogram showing absence of vesico-ureteral reflux. *C*, Postoperative retrograde pyelogram showing diminution in degree of hydroureteronephrosis.

usually necessitate plastic reconstruction of some type; accessory vessels, and bands with fixation, may require division, ureterolysis and nephropexy. Stenoses, however, often are the underlying factor even when vessels and bands are conspicuous.

Vesico-ureteral reflux with normal ureteral orifices and only slight alteration of the oblique course of the ureter through the bladder wall may disappear in time after drainage or removal of some obstructive process in the lower urinary tract. But when the orifices are round and gaping and the ureter passes perpendicularly through the bladder wall, reflux can be stopped permanently only by reimplantation of the ureter, either with or without preliminary section. Figure 35 represents a simple and rapid method especially applicable when redundancy necessitates resection of a long lower ureteral segment. Figure 36, A, is the preoperative cystogram with bilateral reflux; Figure 36, *B*, the postop-

erative cystogram showing absence of reflux; and Figure 36, *C*, is the postoperative retrograde pyelogram showing considerable decrease in the hydroureteronephrosis.

When the ureter is considerably dilated, but not markedly redundant, intravesical implantation of the intact ureter affords satisfactory results. Figure 37 is a simple modification of the procedure used by Hutch[3] for the control of reflux in adult paraplegics. The ureter is not divided, but is merely lifted into the bladder so that the bladder musculature can be sutured behind it. The mucosa and submucosa of the

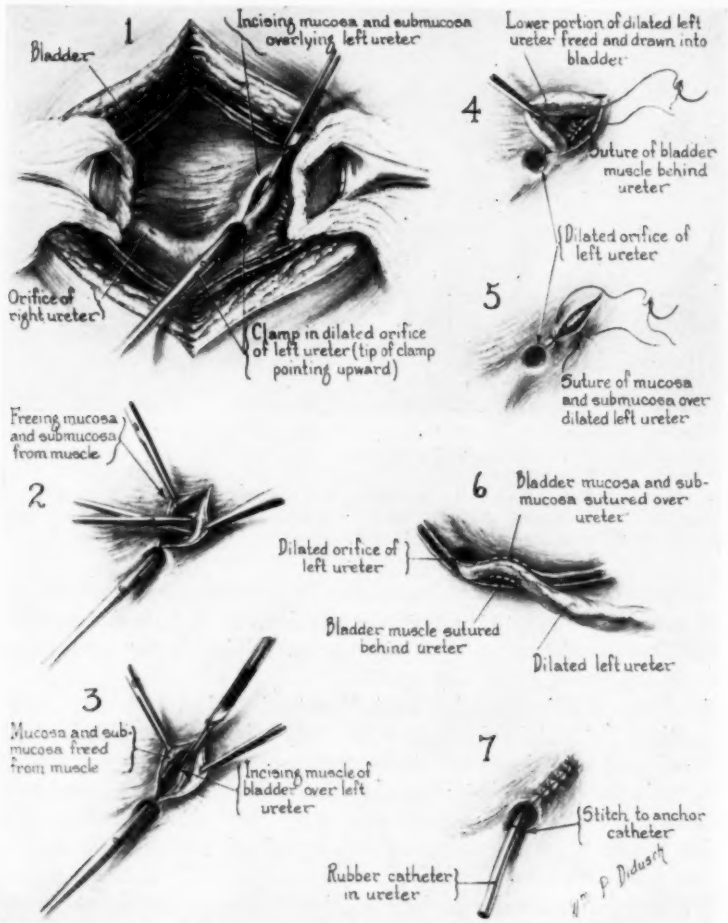
1
Bladder
Incising mucosa and submucosa overlying left ureter
Orifice of right ureter
Clamp in dilated orifice of left ureter (tip of clamp pointing upward)
2
Freeing mucosa and submucosa from muscle
3
Mucosa and submucosa freed from muscle
Incising muscle of bladder over left ureter
4
Lower portion of dilated left ureter freed and drawn into bladder
Suture of bladder muscle behind ureter
Dilated orifice of left ureter
5
Suture of mucosa and submucosa over dilated left ureter
6
Bladder mucosa and submucosa sutured over ureter
Dilated orifice of left ureter
Bladder muscle sutured behind ureter
Dilated left ureter
7
Stitch to anchor catheter
Rubber catheter in ureter

Fig. 37. Author's method of eliminating vesico-ureteral reflux when dilated ureter is not markedly elongated and angulated.

bladder are then sutured together over the implanted ureter. Figure 38, *A*, is the preoperative cystogram showing complete reflux; Figure 38, *B*, the postoperative cystogram without reflux; and Figure 38, *C*, the postoperative retrograde pyelogram showing considerable improvement in the upper urinary tract.

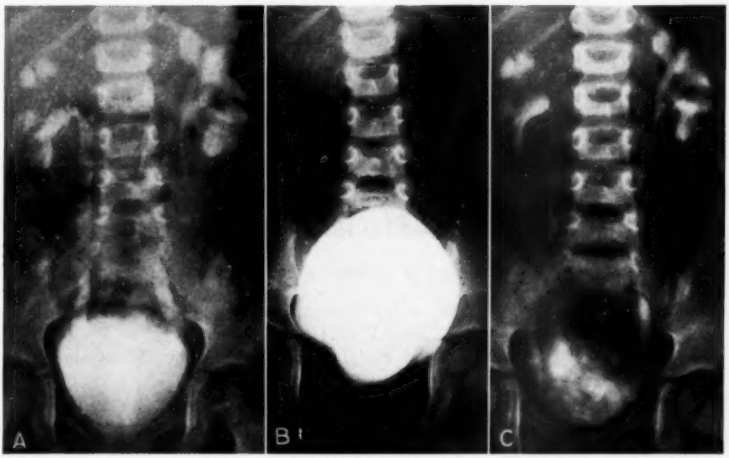

Fig. 38. *A*, Preoperative cystogram of female patient showing complete bilateral reflux of contrast solution with dilated ureters and calyces. This had been gradually progressive despite periodic urethral dilatation. *B*, Postoperative cystogram showing absence of vesico-ureteral reflux. *C*, Postoperative retrograde pyelogram showing decrease in hydroureteronephrosis.

SUMMARY

Most cases of hydroureteronephrosis in infants and children result from mechanical ureteral obstruction or vesico-ureteral reflux of urine, with or without infection. Unilateral obstruction confined to the upper urinary tract may be silent, but pain, gastrointestinal disturbance, fever, chills, toxemia, pyuria, vesical irritability or hematuria should arouse suspicion. When the obstruction is bilateral, anorexia, nutritional disturbances, polyuria, polydipsia and uremia may also appear.

Physical examination may reveal a mass or tenderness, but definitive diagnosis depends on urography. Abnormalities in the blood picture and in the chemical constituents of the blood should be corrected, and the renal function and general condition of the patient improved, if possible before urologic investigation, which may require general anesthesia.

Most cases of obstruction confined to the upper urinary tract in young children require open operation. Conservative surgery, for the

correction of the abnormality and the preservation of renal tissue, or nephrectomy will depend on the judgment and experience of the surgeon, and should be governed by the underlying pathologic condition and the complications it has produced.

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LOWER URINARY TRACT OBSTRUCTIONS IN INFANTS AND CHILDREN

Diagnosis and Treatment

RUBIN H. FLOCKS, M.D.

Lower urinary tract obstructions and their sequelae make up an appreciable percentage of urologic disease in infancy and childhood. Of 828 cases of hydronephrosis in children reported by Campbell, 144 were due to infravesical conditions.[1] Since a large proportion of these obstructions may be diagnosed and treated before hydronephrosis supervenes, this serves to emphasize the frequency of the problem. If one includes neuromuscular diseases of the bladder causing inadequate emptying of the bladder, the problem becomes even more significant. Table 7 shows the acquired and congenital lesions of the urethra and bladder which may produce urinary obstruction in the child. The most important from the viewpoint of frequency

TABLE 7. *Congenital and Acquired Lesions Causing Lower Urinary Tract Obstruction in Children**

URETHRA		BLADDER	
Congenital	*Acquired*	*Congenital*	*Acquired*
Phimosis	Phimosis	Contracture of bladder neck	Contracture of bladder neck
Meatal stricture	Meatal stricture	Median bar	Median bar
Hypertrophied verumontanum	Hypertrophied verumontanum	Diverticulum	Tumor
Diverticulum	Diverticulum	Neuromuscular disease	Prostate enlargement
Hydrocolpos	Hydrocolpos	Trigonal curtain	Calculi
Posterior urethral valve	Polyps	Hydrocele	Extravesical masses
Penile torsion	Trauma		
	Calculi		
	Tumor		

* After Campbell.[1]

and necessity for early diagnosis are urethral stricture, contracture of the vesical neck, ureterocele and neuromuscular disease of the bladder.

SYMPTOMS

In contrast to adults, in whom the local symptoms point to the local disease, lower urinary tract obstruction in children may yield few symptoms pointing to the lesion, or these symptoms may be overlooked.

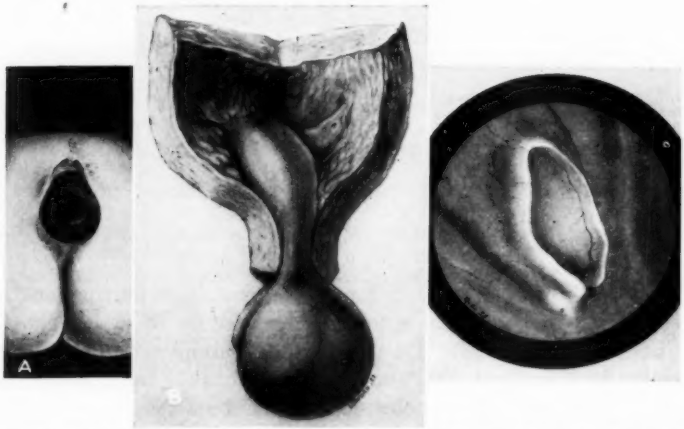

Fig. 39. M.J.H. a female born in 1935, had repeated history of fever and vomiting. She was seen in July, 1935, with an impression of malnutrition, dehydration and possible tuberculosis. On July 26 the urine was negative; history of vomiting and fever. On August 23 the urine contained pus cells; intravenous pyelograms were unsatisfactory. Cystoscopy was not carried out; *it should have been at that time*. Diagnosis of pyelitis and left otitis media was made. Finally the patient came into hospital on April 21, 1938, complaining of a tumor appearing at the vulva, intermittently with associated inability to urinate and intermittent incontinence. Examination shows what appears above in *A* and *B*. Blood pressure was 135/75. The urine was loaded with pus cells. The right kidney showed no function, and cystoscopy revealed an enormous right ureterocele (**C**). This was removed by open operation, after which the blood pressure came down to 110/70. *C*, Illustrating the new appearance of the right ureteral orifice. The right kidney function never returned, however, and a right nephrectomy had to be done to stop the recurring attacks of right pyelitis.

Dribbling and frequency of urination and incontinence due to obstruction or neuromuscular disease of the bladder may be considered simple enuresis (Fig. 39). Crying and irritability before and during the act of urination, changes in the urine itself may all go unnoticed until marked urinary tract damage has occurred. The general symptoms of infection and renal insufficiency, and reflex gastrointestinal disturbances may be the outstanding features leading to medical examination. The lack of growth, nausea and vomiting and secondary anemia all may be the re-

sult of renal insufficiency. Gastrointestinal disturbances may be reflexly caused by difficult urination. Fever and gastrointestinal disturbances may be due to urinary tract infection secondary to stasis. An abdominal mass may be a large, inadequately emptying bladder or secondary hydroureter and hydronephrosis. At times hematuria or pyuria is the manifest symptom. Because of the variability of symptoms and the fact that the general symptoms overshadow the local symptoms, in contrast to the adult, early diagnosis can be made only if the examiner has a high index of suspicion for the possibility of urinary tract disease as the cause for the difficulty in the child and goes ahead with a urologic examination.

EXAMINATION

Physical Examination

The physical examination of a child may give indications of the possibility of the presence of urinary tract disease, particularly lower urinary tract obstructions. Failure in growth may be due to renal insufficiency. Tenderness over the kidneys may be due to the obstructive

Fig. 40. D.F., a 3½ year old boy, was first seen in May, 1953, with congenital bladder neck contracture, absent abdominal musculature, and hydronephrosis. He had 2 transurethral resections of his bladder neck in May and August of 1953, and in July, 1953, a left nephroureterectomy and partial cystectomy were performed. After these procedures he was still unable to void well, and a severe right kidney infection necessitated a right nephrostomy, performed in September, 1953. He has carried this nephrostomy since that time. He has been many times for change of tube; in general, he has tolerated this very well. There has been great general improvement in his condition.

The illustration shows the abdominal appearance of the boy. Note that the loops of bowel can be seen through the abdominal wall. This case is illustrative of the following: (1) the frequent association of absent abdominal musculature with congenital defects of the urinary tract; (2) the frequent need of nephrostomy for relief of renal obstruction.

sequelae of lower urinary tract obstruction. The presence of an abdominal mass may indicate a full bladder. Lack of abdominal musculature is usually associated with congenital anomalies of the urinary tract, particularly contracture of the vesical neck (Fig. 40). Deformities of the external genitalia may indicate obstruction. Stricture of the meatus and deformities of the shaft of the penis frequently go together.

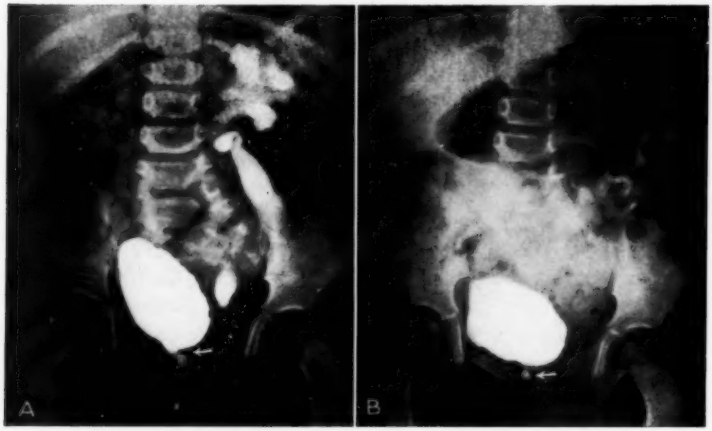

Fig. 41. S.L., a 3½ year old male, born with a meningocele, which was removed at the age of 13 months. This boy has dribbled urine almost continuously and occasionally has complained of pain apparently in the abdomen. On August 6, 1951, his urine was found to be loaded with pus. Cystogram showed a reflux on the left, but none on the right. Intravenous pyelogram showed double kidney on the right with good function and normal appearance. The left showed a marked hydronephrosis and hydroureter. Cystoscopy revealed a flaplike valve at the bladder neck. Thirty centimeters of residual urine was present in the bladder. On August 23, 1951, a Hutch operation was carried out on the left side, and at the same time a plastic operation was done at the internal urethral orifice. He got along nicely after this procedure. Check-up examination in April, 1954, showed prompt bilateral function with no evidence of hydronephrosis on either side, the urine completely clear, and no ureteral reflux—a good result.

A, Shows a retrograde cystogram and urethrogram on this patient prior to operation. Note the deformity at the bladder neck. Note the left ureteral reflux. Note the deformity of the lower end of the spine, indicating the probable presence of neuromuscular disease of the bladder as part of the situation. *B*, Retrograde cystogram after the operation. Note the correction of deformity at the bladder neck and absence of left ureteral reflux.

Rectal examination, particularly bimanual examination under anesthesia if possible, may indicate some type of congenital anomaly in the region of the bladder neck (a bar or contracture may be palpated as a ridge at the base of the bladder) and may make it possible readily to discern a full bladder. In female children this may also demonstrate congenital anomalies producing obstruction at the vesical outlet. This

is an important portion of the examination and is preferably carried out under anesthesia so that muscular relaxation is present and adequate examination can be carried out.

Hypertension, fever, evidences of generalized infection indicate careful scrutiny for a source in the urinary tract, particularly obstruction in the lower urinary tract with the sequelae of this (Fig. 41). Neurologic disease as the underlying basis of the urinary difficulties may be suspected if the anal tone is poor, if evidences of sensory or motor disturbances of the lower extremities or perineum are present and if evidences of congenital deformity of lower spine or sacrum are present. This is also true if the history of acquired conditions of the central nervous system is obtained. Lesions such as congenital syphilis, multiple sclerosis, anterior poliomyelitis, transverse myelitis and injury to the central nervous system may have associated, or as sequelae, neuromuscular disease of the bladder.

Laboratory Examination

This is of extreme importance. The urine should be carefully collected and studied for the presence of pus, organisms and red blood cells and casts. However, a normal urine does not rule out the presence of severe bladder neck obstruction or obstruction elsewhere in the lower urinary tract. Renal function studies, particularly blood nonprotein nitrogen and phenolsulfonphthalein excretion, are extremely important, can be done readily, and may be helpful in deciding the future course of the examination. Renal function studies, however, may be entirely normal in the face of severe bladder neck obstruction if the latter is diagnosed early, before upper urinary tract damage has occurred.

Roentgen Visualization

Visualization of the urinary tract by means of roentgenography is of great importance in the examination of patients with lower urinary tract obstruction. Frequently much information can and should be gained without instrumentation. A plain film may indicate the presence of a mass in the lower abdomen, indicating a full bladder; it may give evidences of a spina bifida and indicate the possibility of neuromuscular disease of the bladder and the underlying cause of the difficulty (Fig. 41); it may show the presence of a calculus as the cause of the obstruction (Fig. 42) or may show evidences of disturbance of bony growth secondary to renal insufficiency.

If the renal function tests, particularly the nonprotein nitrogen, are within normal limits, intravenous pyelography, or intramuscular pyelography if the veins are hard to inject readily, is of great value in these

cases. Dehydration overnight with the administration of food and fluid to fill the stomach with fluid and air just before making the film is of value in getting the best pictures—pictures that are the least obscured by gas. Fifty per cent Urokon or 30 per cent Diodrast may be used either intramuscularly or intravenously. If they are used subcutaneously and intramuscularly, injection with 75 turbidity units of hyaluronidase is of advantage in securing rapid absorption of the radiopaque material. Exposure is made at three, four and five minute intervals, and the pictures are examined as they are exposed so that the length between future

Fig. 42. Plain film of the region of the bladder in a male child of 3 years, complaining of dysuria and hematuria. Note shadow in region of urethra. This turned out to be a cystine stone.

exposures and the securing of excretory cystograms and urethrograms can be carried out adequately.

Frequently the character of the bladder wall, the amount of residual urine, the outline of the bladder neck and information about the urethra may be readily obtained by means of an excretory cystogram and urethrogram immediately after the visualization of the upper urinary tract. The urethrogram is obtained by placing the patient's pelvis at a 30 degree angle to the table containing the film, and, with the downside thigh flexed and the upside thigh extended, have him urinate into a container as the film is exposed. This makes an excellent "voiding urethrogram." If the bladder is large and full and the bladder wall is markedly trabeculated, evidence of obstruction or neuromuscular disease is clearly indicated.

Filling defects in the bladder associated with ureterocele or tumor may at times be visualized by means of excretory cystography just as well as by means of retrograde cystography and urethrography. Hydro-

nephrosis and hydroureter can frequently be indicated readily by this means, and the presence of such an abnormality may mean either coincidental, congenital obstruction of the ureter or congenital malformation of the kidney pelvis or kidney, or may mean simply back pressure effects from lower urinary tract obstruction.

Instrumental Examination

Upon completion of the physical examination, the laboratory examination and visualization of the urinary tract by means of plain film or excretory pyelography, cystography and urethrography, it may well be that a tentative diagnosis can be readily made about the presence or absence of a lower urinary tract obstruction, and some indication is at hand of the nature of this obstruction and of the sequelae which have resulted from it. Frequently, however, instrumental examination is necessary in order to gain more information about the lesion itself and the nature of the sequelae. Instrumentation should be done in such a manner that the least trauma and the most information can be gained from it.

Instrumental examination practically always, except in rare circumstances in older female children, necessitates anesthesia. It is of great value, in my opinion, to use anesthesia when instrumentation is carried out, for the following reasons. Firstly, it is possible to do an adequate bimanual examination, which is an important part of the physical examination in these cases. Secondly, instrumentation can be carried out gently, and this is extremely important when dealing with the delicate structures of the child, since trauma may well induce stricture formation in the future. Thirdly, the deformities which are present are varied, the instruments used are small, and careful interpretation of the results of the findings is difficult if the patient is moving and the examination has to be carried out under handicaps of movement of the patient and time limitations.

Simple passage of filiforms and bougies or catheters into the bladder gently will indicate the presence of a stricture anywhere along the urethra and will indicate also the presence or absence of residual urine in the bladder. Repeated residual urine of over 20 cc. in these small children is usually indicative of obstruction or detrusor weakness. Retrograde cystography and urethrography may be of great value (Fig. 43). Cystography will indicate the size of the bladder, the character of the bladder neck and of the bladder wall, the presence or absence of diverticula and filling defects, the presence or absence of ureteral reflux either secondary to the bladder neck obstruction, which will need to be cared for at a later date, or as an associated anomalous situation in the

Fig. 43. G.A.S., a seven year old boy, was admitted to the Genitourinary Service on January 26, 1951, with a complaint of wetting his bed. Intravenous pyelograms showed good function bilaterally with dilatation of the lower halves of each ureter. This was suggestive of obstruction of the bladder neck from residual urine in the bladder. Cystoscopy was performed on January 29, 1951, and a median bar deformity of the bladder neck was found. Transurethral resection of this bar was carried out. After this the patient voided with a satisfactory result and began to empty his bladder completely. This is an example of good result by transurethral methods. Note that the symptomatology was that of enuresis.

The retrograde cystourethrogram shows the characteristic anterior tilting of the bladder neck caused by the median bar.

lower ureter. At times delayed cystography is necessary before a ureteral reflux will become manifest in early or slightly involved cases.

If necessary, retrograde pyelography associated with urethroscopy and cystoscopy may be performed. The latter are extremely helpful to visualize the prostatic urethra, an enlarged verumontanum, valvelike flaps in the prostatic urethra, valvelike flaps, ureterocele, tumor and other deformities of the bladder itself, the changes at the bladder neck associated with bladder neck contracture, tumor, and so on. Exploration of fistulas or accessory urethras may readily be carried out under anesthesia with ureteral catheters or filiforms and bougies.

NEUROMUSCULAR VESICAL DYSFUNCTION

Neuromuscular vesical dysfunctions may be classified as illustrated in Table 8. In the presence of dysuria of any type, particularly with incontinence or inadequate emptying of the bladder even with, but more so without, the demonstration of a congenital obstructive lesion, it is necessary seriously to consider congenital, acquired or idiopathic neuromuscular disease. Spina bifida occulta usually is of no significance, but more extensive deformities of the lower spine and sacrum (see Fig. 41) are usually associated with lesions of the lower cord or sacral roots or nerves. Acquired lesions usually are more evident from the history. Careful neurologic examination, typical cystometrograms if these can be performed, the wide open bladder neck on the cystogram, the presence

TABLE 8. *Classification of Neuromuscular Vesical Dysfunction*

I. CONGENITAL
- A. Malformation or dysplasia of central nervous system and peripheral nerves
- B. Malformations, pathogenesis not clearly understood, of nervous structures within bladder

II. ACQUIRED
- A. Disease or injury of central nervous system
  1. Infection (anterior poliomyelitis, syphilis, etc.)
  2. Due to poisons or toxins
  3. Trauma
  4. Tumors
  5. Degenerative lesions such as syringomyelia
- B. Unknown (idiopathic)

of a large, slightly trabeculated bladder wall should all indicate the possibility of obstruction on a neurogenic basis. The late sequelae are similar to those associated with long-standing obstruction due to mechanical causes.

After the decision has been made that there is a neurogenic component to the urinary difficulties which the patient exhibits, three questions need to be considered: (1) What is the type and course of the underlying neurologic disorder? (2) Is there a large amount of residual urine in the bladder? (3) Is there incontinence or dysfunction without residual urine in the bladder and without any evidences of obstructive sequelae in the bladder or upper urinary tract? Neurologic and urologic surveys as outlined in the previous paragraphs will, in most instances, answer these questions adequately, particularly the last two.

The type and course of the underlying neurologic disorder will be important factors in the prognosis and in the type of urologic therapy to be instituted. If the neurologic disease is permanent and possibly slowly progressive, then transurethral bladder neck resection or other irreversible therapeutic procedures may be carried out. On the contrary, if it is hoped that the condition will clear up in a few months or if lami-

nectomy and surgical treatment to the cord structures is being contemplated, then intermittent catheterization, nephrostomy, cystostomy or the smallest, most reversible procedure should be done upon the urinary tract. This should be consistent with obtaining good drainage and control of infection until the results of direct therapy on the lesion of the central nervous system are known.

Treatment

If neuromuscular disease is the factor behind a flaccid bladder with large amounts of residual urine and back pressure effects such as are seen with anatomic obstruction, trabeculated bladder, ureteral reflux, large tortuous ureters, hydronephrosis, pyonephrosis and renal insufficiency, the urologic therapy is similar to that outlined below.

Adequate drainage and control of infection must be sought for at all costs. Bilateral nephrostomy may need to be done first because of the presence of ureteral atonicity, tortuosity and reflux. Partial removal of a large flaccid but thickened bladder wall may be necessary. On the contrary, if evidences of back pressure effects are lacking, simple transurethral resection of the internal sphincter to weaken it somewhat or the administration of Mecholyl in small doses will cause the bladder to empty. Sometimes the simple development of an automatic reflex bladder aided by manual compression in the suprapubic region at regular intervals will suffice. If the neurologic difficulty is spasticity or a weakness of the sphincters without the presence of residual urine in the bladder, infection and back pressure effects need not be feared. In such cases incontinence with social disability, excoriations of the skin of the perineum and bedsores are the pressing problems. The treatment is directed primarily towards decreasing spasticity of the detrusor muscle and increasing the strength of the sphincters. In some instances drugs may solve the problem. Banthine in 25-mg. doses once or twice a day associated with ephedrine, ⅜ grain in divided doses given orally, may be useful. Fascial and muscle transplants to control incontinence in these cases are rarely successful (Campbell[1] reports several good results using rectus muscle).

Recently more attention has been placed on the use of the anal sphincter in those instances in which it is not involved and can be conveniently used. In general these operations prove to be failures, and prostheses of various sorts with or without the diversion of the urinary stream may become necessary. The Cunningham clamp may prove useful in the male. Suprapubic cystostomy with suture of the urethra may be successful, and occasionally in order to keep the patient free of bedsores cutaneous ureterostomy may be necessary. In the badly involved cases with much incontinence, certainly before ureteral diversion of the stream is performed, serious consideration should be given to

cordotomy, cordectomy or rhizotomy to create a flaccid type of bladder. This type of bladder then can be drained regularly by training and manual suprapubic compression at regular intervals or by a suprapubic cystostomy, which would not work satisfactorily in a markedly spastic bladder.

TREATMENT

After a complete examination a diagnosis can be made in practically 100 per cent of the cases of the presence or absence of an obstructive lesion of the lower urinary tract. The nature of this lesion can be thus well demonstrated. It is important in addition to this to elucidate whether or not there are associated congenital lesions of other portions of the urinary tract, particularly of the upper urinary tract (this is frequently present). Also, of even greater importance is the necessity of accurately assessing the sequelae from this obstruction producing dilatation of the urinary tract proximal to the lesion and, associated with this dilatation, infection, diverticulum formation, stone formation and renal insufficiency, which may need to be overcome before or as part of the management of the local lesion.

If lower urinary tract obstruction has been present for a significant length of time and is associated with marked ureteral reflux and bilateral hydroureter and hydronephrosis with infection, simple repair of the obstruction below may not be enough to solve the patient's difficulty. He may continue to have recurring bouts of upper urinary tract infection and progressive damage to his upper urinary tract, even though the obstructive lesion in the lower urinary tract has been removed satisfactorily. Moreover, the immediate morbidity and mortality following the attempted surgical removal of the lower urinary tract obstructive lesion will definitely be higher unless this upper urinary tract damage and difficulty is considered. It may well be best in many cases to do a bilateral nephrostomy prior to surgical correction of the distorted ureters, the distorted bladder and the obstructive lesion itself (Fig. 44). The marked dilatation and distortion of the ureters which is frequently associated with such bladder neck obstructions must be corrected per se and rarely improves upon removal of the bladder neck obstructive lesion itself. For this reason there has been an increasing trend in our own practice at the University Hospitals to pay increasing attention to the sequelae of such bladder neck obstructions and start the therapy from above downwards, rather than from below upwards, in those children who have severe distortion of the ureters and kidneys secondary to bladder neck obstruction.

If ureteral reflux is present without greatly distorted ureters, it may well be that correction of the ureteral reflux by the Bunts-Hutch procedure or some modification of it, associated with sidetracking of the

urine by means of a suprapubic cystostomy until correction of the lower urinary tract obstruction seems feasible, may be the first procedure. If, on the other hand, there is marked distortion of the kinking of the ureters associated with ureteral reflux, bilateral nephrostomy may be the first procedure. The second procedure may then be correction of the bladder neck difficulty with or without the correction at this stage

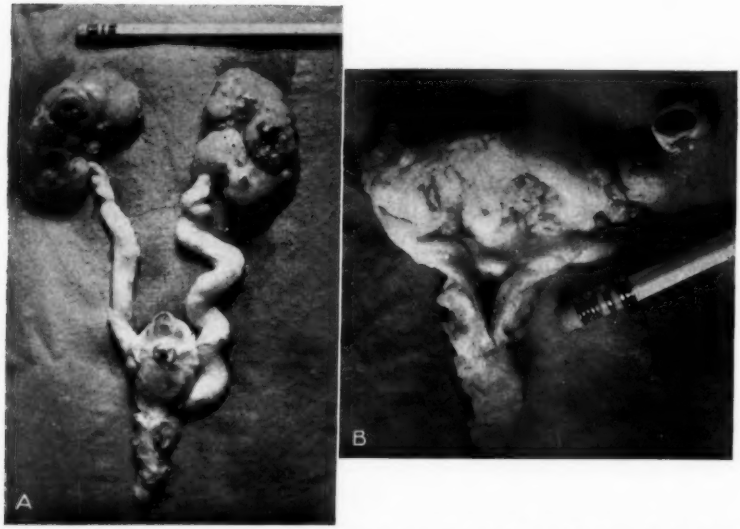

Fig. 44. E.M.F., a 4 months old patient, began having trouble during the first month of life. There was an unexplained afternoon fever which was noted to be on a dietary basis. He entered the hospital on January 4, 1944. Nonprotein nitrogen was 123 mg. Suprapubic cystostomy was done on January 17, 1944. Postoperative course was stormy. Would not a nephrostomy have been better in this case? In similar cases good ultimate result is obtained after preliminary nephrostomy.

A, Gross appearance of bladder, ureters and kidneys post mortem. Note thickened bladder walls, dilated, thick-walled, tortuous ureters, and dilated kidney pelves with abscesses in thinned renal cortex. B, Bladder incised to show contracted bladder neck.

of the ureters themselves. At this time a poorly draining diverticulum of the bladder should be removed. Then, at a third stage, plastic straightening of the ureters with neo-ureterocystoplasty is carried out in such a way as to avoid ureteral reflux.

If unilateral reflux and hydroureter and hydronephrosis are present and the other upper urinary tract is perfectly normal and there is not too much trabeculation of the bladder wall, it may well be that the condition is not primarily due to back pressure effects, but is due to an associated congenital anomaly. In such instances nephroureterectomy may be the treatment of choice after satisfactory correction of the bladder neck obstruction has been achieved (Figs. 45, 46, 47 and 48).

A second great trend in the management of children with lower urinary tract obstructions has been evident in the past several years. This has been the increasing use of the suprapubic and retropubic approaches for the management of many of the conditions producing obstruction at the bladder neck. Many conditions such as hypertrophied verumontanum, small polyps, and valves in the urethra are readily cared for by the use of the infant resectoscope or cystoscope with coagulation

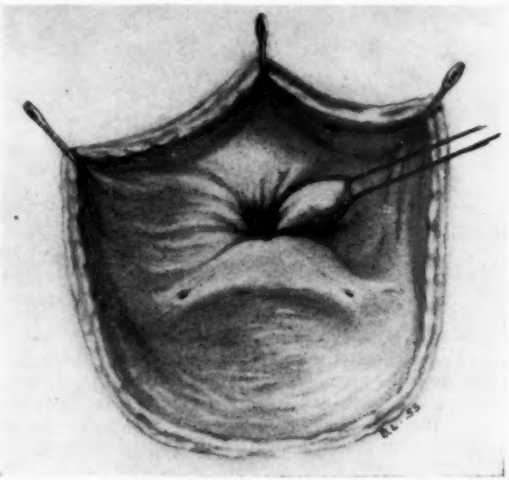

Fig. 45. D.L.H., a male, was seen at the age of 11 months with straining on voiding and crying during voiding. Cystoscopy revealed a tumor mass at the bladder neck. This was a small papilloma, which was removed, after which the patient got along splendidly. Diagram of appearance of bladder neck at time of suprapubic removal of papilloma. Because of the patient's age and consequent small size of the urethra, it was felt that the tumor could be removed more safely and with less risk of later complications, such as urethral stricture, by open procedure. Good result.

of the obstructing lesion, using a Bugbee type of electrode. However, other conditions, particularly bladder neck contracture, are not always satisfactorily treated by the transurethral route. Even with multiple resections as recommended by Thompson and Emmett apparently not all the obstructive tissue is removed, or secondary scarring following the operative procedure remains to maintain bladder neck obstruction. Moreover, increasing recognition of the importance of correction of the sequelae or associated anomalies connected with the bladder neck obstruction, necessitating open operative procedures, has produced an increasing tendency to treat these bladder neck obstructions by open surgery. This is readily carried out in these children with modern methods of anesthesia and chemotherapy of urinary tract infections. They tolerate catheters well, and the procedures can be carried out just as readily as in the adult.

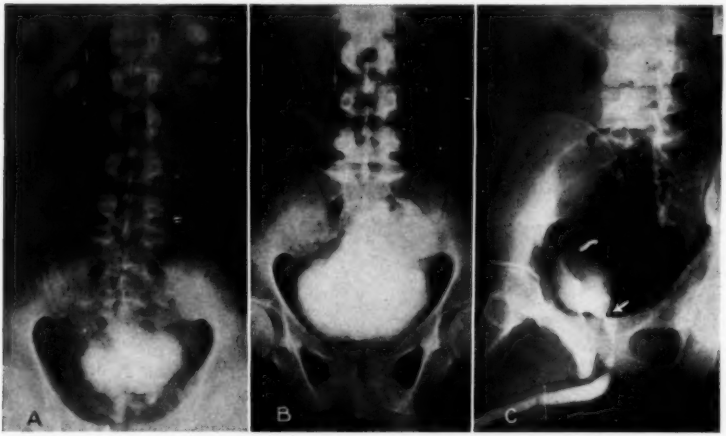

Fig. 46. R.S., a 21 year old man, entered the hospital complaining of recurring attacks of "pyelitis" all his life. Urine loaded with pus. Rectal tone was good. Prostate did not feel abnormal. There was 300 cc. of residual urine in the bladder. Intravenous pyelograms (*A*) show bilateral hydroureter and caliectasis with irregular bladder wall on the cystogram. *B*, Retrograde cystogram shows 2 large diverticula of the bladder. *C*, Urethrogram shows bladder neck contracture.

This patient had a diverticulectomy and revision of the bladder neck contracture all done in one stage through a suprapubic approach. Good result. This is illustrative of bladder and upper urinary tract damage due to failure to make an early diagnosis.

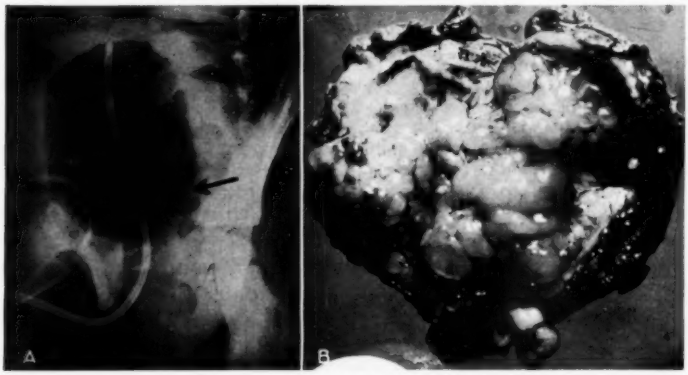

Fig. 47. J.S., a 6 year old boy, entered the hospital complaining of frequency, painful urination and bloody urine. Cystogram, illustrated in *A*, showed a filling defect on the posterior wall. Cystoscopy revealed typical myxosarcoma of the bladder—appearance of clusters of grapes. Total cystectomy and bilateral uretero-intestinal anastomosis were done in November, 1946. Good result. Specimen illustrated in *B*.

The surgical approach to the bladder, in my opinion, is best made in most instances through a transverse suprapubic incision just above the symphysis which, after dividing the lowermost portions of the recti muscles, can be curved upward on each side to give a wide exposure of

the entire bladder and the lower one third to one half of the ureters on each side. Whatever procedure is necessary in this region can be easily carried out. For bladder neck contracture an inverted Y-shaped incision is made, the stem of the Y going vertically through the anterior wall of the urethra and the two stems starting at the bladder neck and pro-

Fig. 48. Urethrogram illustrating traumatic stricture of the anterior urethra. Corrected in two stages by the Johanson procedure with excellent result.

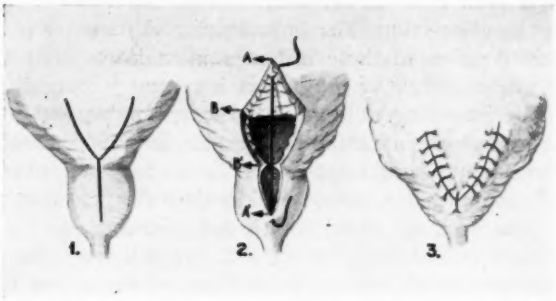

Fig. 49. Diagram illustrating technique of widening bladder neck by using a bladder flap.

ceeding upward, completely incising the bladder wall on each side and thus allowing wide exposure of the bladder neck. Scar tissue at the bladder neck is excised and the tongue of the Y sutured to the distal-most portion of the incision in the prostatic urethra so that the bladder neck is widened by the flap of bladder wall. This technique, described by Young[4] and Nesbit,[3] is useful in both congenital and acquired bladder neck contracture (Fig. 49). It is our practice to drain the bladder suprapubically through a stab wound for about six to ten days to permit repair of the bladder neck without tension.

It is perfectly feasible, if the general condition of the patient is good and if the upper urinary tract and renal function has been satisfactorily improved and maintained, to carry out a partial cystectomy or some type of ureteroplasty or diverticulectomy at the same sitting. On the other hand, if upper urinary tract damage is present and has not been controlled by an indwelling catheter or suprapubic cystostomy, nephrostomy may be the first operation, as indicated previously. Later, operative attack upon the lesion will be indicated.

SUMMARY

A discussion of lower urinary tract obstructions in children and their diagnosis and treatment has been given. The great variety of lesions which may produce such obstructions has been outlined. The techniques available for their early recognition—their variable symptomatology, and the important points of the physical examination, roentgen examination and instrumental examinations in these patients—have been described. The necessity of maintaining a high index of suspicion in children with misleading symptoms and signs is emphasized because early diagnosis of these lesions is necessary to salvage the urinary tract which is the seat of an obstructive lesion.

Two new trends in the management of these patients are emphasized. The first is the increasing realization of the necessity of correction of the sequelae prior to or in conjunction with correction of the lesion producing the obstruction. The importance and necessity of drainage of the kidney pelves in those instances in which marked distortion and/or excessive kinking of the ureters is present is emphasized. The second is the increasing utilization of the retropubic and suprapubic approaches to correct lesions at the bladder neck. In this connection, stab wound suprapubic drainage of the bladder to insure better healing of suture lines and utilization of bladder flaps for plastic enlargement of the bladder neck are useful additions to the urosurgical armamentarium.

The management of neuromuscular disease of the urinary bladder is briefly outlined.

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ACUTE URINARY TRACT INFECTIONS IN INFANTS AND CHILDREN

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A study of the pathogenesis of acute urinary tract infections in children might not be necessary today, except for purely academic purposes, had modern advances in the development of antibacterial agents truly satisfied the goal of Ehrlich. Research in this field during the past decade has indeed done much to support the view that man has at last placed himself in a position to control his unfavorable bacterial environment. Yet the observations of responsible investigators during these last ten years have done little to support the aura of panacea which originally cloaked the antibiotics and chemotherapeutic agents at the time of their introduction.

It is apparent that these agents have done much to improve the infant's chance to survive and reach natural life expectancy. It is also apparent that the administration of antibacterials is associated with almost as many new problems as old ones solved. Allergic or toxic reactions often occur. Some of these are minor and can easily be controlled or, if not, can be tolerated by reason of the benefits that are expected. Others are more severe and contraindicate the use of the agent altogether. More important still is the occasional complete therapeutic failure and the not infrequent evolution of adaptive or mutant bacterial strains which in turn pose an increased problem of therapy.

An intelligent approach to the management of urinary tract infections at any age must therefore include a philosophy of therapeutic failure as well as success. Both attitudes must be based on an understanding of the pathogenesis of infection as it applies to the urinary tract. Only in this way will the physician escape the ignominy of automaticity that seems often to characterize the prevailing attitude toward antibiotic therapy.

The treatment of acute urinary tract infections in children must be based, then, on an understanding of the problem as a whole, and must encompass an awareness of the common avenues of approach pursued by the various bacterial invaders, the natural response engendered in both the host generally and tissue locally, the expected course of the disease if unchecked, and finally the various means available for investigation and ultimate control.

It is perhaps a credit to the passively acquired immune processes of the infant that he is able to survive the transition from the protected sterile environment in utero to the microscopically, and sometimes grossly, contaminated world in which he finds himself. It is of interest that this adjustment is quickly made, and for all practical purposes both infant and adult face many common problems in the constant battle between an intact, unspoiled genitourinary tract and the outside environment.

Both ages, for instance, share certain factors which may predispose to recurrent inflammation. Thus the anatomic misfortune of a short urethra has condemned the female child and the female adult to the constant hazard of bacterial contamination, the former by reason of prolonged contact with a soiled diaper, the latter through assumption of active sexual life, the trauma of childbirth and later on the vagaries of vaginal hygiene attendant on senility.

The male child, by contrast, remains relatively free from lower urinary tract infections. Though not rare, infection at this time in this sex is so uncommon that its presence should automatically arouse suspicion of some underlying, unrecognized factor which might, by reason of its presence, contribute to the existence and perpetuation of infection. It is only on assumption of sexual maturity that the male, too, encounters the common hazards of his environment. It is at this time that the urethra and accessory sex glands may prove stepping stones for the logical progress of infection into the urinary system.

The natural orifices of the genitourinary tract may thus provide a main avenue of access for bacterial invaders. The other primary route, the hematogenous one, is quite different both in manner of approach and the type of organisms involved. A consideration of pathogenesis lends itself, therefore, to a division into two important categories.

HEMATOGENOUS COCCAL INFECTIONS

Approximately 25 per cent of acute infections of the urinary tract in children of both sexes are caused by coccal organisms. *Micrococcus pyogenes* is the most common offender, the hemolytic and green-producing streptococci less common, and *Streptococcus fecalis* still more rare.

Kidney Infections

Acute staphylococcal infections of the kidney constitute a distinct and important clinical entity, certain characteristics of which tend to obscure its early diagnosis. As a consequence, in the past, the disease was usually recognized through its complications, namely, renal carbuncle, perinephric abscess or contiguous basilar pneumonitis.

The portal of entry leading to hematogenous spread is variable. The cutaneous furuncle, the mucous membrane insulted by an acute upper respiratory infection, or a deep-seated smoldering suppurative process in some other organ structure may provide the start. Urethral catheterization or the introduction of a cystoscope occasionally accounts for the presence of *Streptococcus fecalis* in the blood stream. In many instances no primary lesion can be demonstrated to account for the end result, suggesting that the actual portal of invasion may be so insignificant as to escape notice.

The initial renal parenchymal insult is concentrated in the cortical zone of the kidney, where vascular supply is most abundant, a fact which no doubt accounts for the high incidence of early and complete healing which characterizes this infection. Grossly, the kidney is enlarged from congestion and edema. Multiple small areas of suppuration may be seen scattered throughout the cortex. They may coalesce to form small and then large *abscesses*. Some eventually group to occupy a large portion of the parenchyma; this form is known as a *renal carbuncle*. Others rupture through the capsule into the perinephric area, or extend there via the perirenal lymphatics, and rapidly involve the entire perirenal capsule and the fat within the confines of Gerota's fascia. The abscess may extend beyond the limits of this barrier and point in Petit's triangle, or travel downward along the course of the ureter and come to the surface at the external inguinal ring, may extend deep in the pelvis and point in the perineum by way of the ischiorectal fossa and occasionally rupture into the bladder. The infectious process may also travel from the superior pole of the kidney through the diaphragm and incite a contiguous pleural reaction above with pleuritis, *pneumonitis* and lung abscess, and, if the bronchi are involved, create a perinephrobronchial fistula.

Symptoms. The patient so involved is usually septic from the start with abrupt onset of chills, fever and constant perirenal pain, sometimes so severe as to simulate renal colic. True costovertebral angle tenderness is almost always present. Bladder irritation is uncommon, a fact which may confuse the physician taught to suspect renal inflammatory disease only in the presence of cellular urinary reaction. The patient with acute staphylococcic kidney almost never has increased frequency of urination and experiences no dysuria during the early stages of the disease. Leukocytosis is always high; the urine may show a trace of albumin, a few red blood cells and, as stated, no white blood

cells. The physician usually does not suspect the showers of staphylococci that exist during the first few days of the disease and may thus fail to make an examination of the centrifuged stained urinary sediment and so completely miss the bacteriuria. Secondary invasion of the urinary tract by bacilli occurs in about 30 per cent of the cases of coccal kidney; coincident with this, pus is found in the urine, bladder irritative symptoms begin, and, interestingly enough, the coccal forms previously abundant are often no longer found, perhaps unable to compete in the same environment with the new dominant microorganism.

Course. In the days prior to antibiotic and chemotherapeutic agents acute staphylococcal infection of the kidney pursued a stormy, self-limited course lasting from seven to 14 days, during which time the normal body immune response could be expected to bring the process under control, barring extension of the disease to surrounding structures. The current widespread use of antibacterial agents in acute febrile states has undoubtedly contributed to the fact that acute staphylococcic kidney is now seldom seen. The same may be said of renal carbuncle and perinephric abscess. Nevertheless, even today, failure on the part of the patient to seek timely medical advice or failure on the part of the physician to recognize the entity in its early stages leaves a certain residual which prevents exclusion of this disease from modern tests on differential diagnosis. The ever-increasing numbers of penicillin-resistant, gram-positive staphylococci in our present environment will undoubtedly do much to return this interesting entity to its former incidence of occurrence.

Treatment. There is of course no substitute for needed surgical drainage once abscess formation has occurred. However, the goal of the physician is early recognition and early institution of therapy, anticipating resolution of the process before complications develop. If then the classic signs and symptoms of acute perinephritis are accompanied by a sudden coccal bacteriuria, it is reasonable to commence treatment at once. In view of its recently acquired shortcomings, penicillin is no longer the drug of choice in infections caused by gram-positive micrococci. Both Erythromycin and Magnamycin appear, for the moment, to be reasonable substitutes and may be expected to resolve the majority of such infections if given in good dosage over a sufficiently long time. The streptococci, except *Streptococcus fecalis,* still show a reasonable degree of sensitivity to penicillin. However, the effective spectrum of Erythromycin includes these bacteria, and so it is best to start treatment without waiting for the results of cultural identification.

BACILLARY ASCENDING INFECTIONS

The gram-negative bacilli account for 75 per cent of the infections of childhood. The most common organisms are members of the coliform

group, less frequently *Aerobacter aerogenes*, and in the order of decreasing frequency, *B. proteus*, *Ps. aeruginosa*, Salmonella, Shigella and Alkaligenes. Reference has already been made to the secondary bacillary invasion of the coccal kidney.

Bladder Infections

Commonly these organisms gain access to the upper urinary tract after first establishing themselves in the bladder. Initial symptoms then may be those referable to the bladder, again often abrupt in onset with increased frequency of urination, dysuria, suprapubic pain and occasionally, at the height of the inflammatory reaction, a vesical congestion so severe that bleeding occurs. The infection may then be termed a *hemorrhagic cystitis*.

Diaper contamination and later on improper toilet habits may promote urethral infection followed by cystitis in the infant. Cystitis may also accompany acute respiratory infections or the "flu," in these instances perhaps as a secondary invader during a period of reduced general resistance. Bacillary bladder infection may also follow urethral instrumentation. Gentleness and aseptic technique are of course accepted requirements when urethral catheterization is necessary, but often despite these precautions bacterial invasion may accompany the performance of this simple operation and give rise to sequelae so severe that the physician, in retrospect, concludes that catheterization does not belong in the category of the "routine," but must be reserved for those diagnostic or therapeutic circumstances in which the information or benefits gained outweigh the inherent risks.

Kidney Infections

Pyelonephritis. Unfortunately at least one in every ten patients with acute inflammation of the bladder has ascending infection of the kidney as well. This complication is ushered in by sudden onset of kidney pain, chills, fever, often profound sepsis, and a marked increase in the already high white blood cell count. There has always been considerable speculation as to just how this invasion is accomplished. It seems likely that it is a process of direct extension into the ureter and then rapidly on up into the collecting system. The periureteral lymphatics have been implicated by many investigators as a possible alternate route, but there is no convincing proof that this is so. The lymph channels pursue no direct path to the kidney, but are, instead, segmental and drain into the regional nodes at various levels above the bladder. Whatever the route, the process is a swift one, so swift in fact that the older term "pyelitis," implying an entity characterized by inflammation of

the renal pelvis alone, has largely been replaced by the general term "pyelonephritis," for in reality the infection is a generalized disease of both parenchyma and collecting system almost from the onset.

If inspected grossly at the height of the infection, the kidney presents a swollen, congested appearance and looks almost purple on cut section. The perinephric fat surrounding it will be markedly edematous. It is easy to understand how such a kidney, taut within its capsule and surrounded by acute inflammatory reaction, may give rise to both pain and costovertebral tenderness. The renal pelvis may be filled with exudate, and the ureter as well demonstrates a severe pyogenic response. A kidney so affected rarely suffers the complete local destruction characteristic of the advanced stages of staphylococcal infections (renal carbuncle). Instead, the process either resolves, leaving little or no evidence of its presence, or becomes chronic.

It is not difficult to recognize a full-blown acute pyelonephritis; if treated properly, it may be expected that the majority of cases will resolve without difficulty.

EFFECT OF TREATMENT. Proper treatment of course implies that the therapeutic agent must be administered in an amount which will be effective in all parts of the renal parenchyma where the infection is located. Some investigators in the past gauged dosages of antibacterial agents in terms of effective urinary concentration. This is a fallacious practice, since the urine is a concentrate of products contained in the blood serum. Effective therapeutic dosages must be gauged rather on the serum level of the drug. In short, antibacterials should be given in large amounts if given at all, not sparingly.

Failure to respond promptly should lead the physician to wonder whether the child does, in fact, have a simple case of pyelonephritis or whether the infection is rather a complication of some condition involving stasis. Appropriate investigations will usually determine this point. But there is a certain small percentage of cases in which kidneys, previously normal, will remain infected after the period of acute sepsis has abated. They go on to a chronic phase and fail to heal, perhaps by reason of the response of the invading organism to the drug that has been used, or the manner in which the agent was given.

It is of even greater concern that about 30 per cent of cases of chronic pyelonephritis are not preceded by a violent systemic reaction, and therefore may escape the notice of both physician and patient. The infant is, of course, unable to communicate the exact nature of presenting symptoms. Systemic irritability may easily be passed off as a "teething problem," and bladder irritability may be camouflaged by the ever-present diaper. In such circumstances the first evidence of the disease, if unilateral, may be the development of hypertension in early adulthood, or, if bilateral, the signs or symptoms of renal failure.

As a rule chronic active pyelonephritis pursues an inexorable course characterized pathologically by infundibular calyceal stenosis with hydrocalycosis and atrophy of the renal tubules. Eventually even the glomerular structures are involved. Contracture occurs owing to scar present in a patchy fashion throughout the substance of the kidney as the disease wreaks havoc at varying rates of speed in separate areas. If the inflammation is arrested by natural immune processes, the term "chronic healed pyelonephritis" may be applied and implies a cessation of progression with stabilization of renal function at that level. If activity continues, however, it may be predicted that chances for control with presently available antibacterial agents are poor, for experience has shown that less than 10 per cent of patients respond even to vigorous therapeutic programs, and many of these relapse after temporary benefit.

It is obvious from the preceding discussion that the terms "chronicity" and "therapeutic failure" are often synonymous. It is important that the physician adopt a philosophy of therapy so designed as to avoid the common pitfalls that lead to chronic inflammatory reaction. Fortunately the majority of acute bladder infections are recognized at once by reason of the severity of irritative symptoms they produce. An examination of the sediment obtained from a centrifuged urine specimen will disclose the presence of pus, and a simple stain will identify the organism as either coccal or bacillary. Since the majority of uncomplicated bacillary infections respond to sulfonamide preparations, it is reasonable to give a drug representative of this group, such as Gantrisin, in effective dosage over a period of time. If symptoms subside and the urine remains free from pus and bacteria on two successive examinations at weekly intervals, it may be assumed that treatment was successful.

Most urinary infections fortunately have this happy outcome. Those that do not are the ones which throw a grave responsibility upon the attending physician. He must find the reason for the continuing infection and correct the situation if the child is to be spared a lifetime of crippling disease. There are many causes for chronic infection: resistance on the part of the organism to the drug used, obstructive uropathy or neurogenic disease which interferes with normal drainage within the urinary passages, calculous disease, unsuspected urinary tuberculosis, chronic suppurative renal disease, neoplasm. To expend valuable ammunition in the form of broad-spectrum antibiotics at this stage of the treatment program is but to invite total therapeutic failure, for conditions are obviously present which mitigate against success. No drug, however satisfactory, can pass the barrier of chronic inflammatory reaction to reach bacteria in effective concentrations at the sites most needed. No agent can penetrate the interstices of a jagged stone and

search out organisms, nor can it reach the base of a necrotic neoplasm to promote bacteriostasis. Instead, bacteria so treated are subjected to a diminished concentration needed to bring about their control; they adapt themselves, give rise to resistant mutant strains, and form new progeny which are not only unaffected by an agent previously lethal, but in some instances are actually enhanced by its presence.

URINARY TRACT EXAMINATIONS

The next logical step, before further treatment is instituted, must therefore be a thorough investigation of the urinary tract, including endoscopic inspection of the urethra, cystoscopic evaluation of the bladder, retrograde ureteral catheterization and collection of urine specimens from each kidney, and finally retrograde pyelography. Once a contributing factor is found, its removal must be effected before additional antibacterial therapy is begun on the basis of cultural identification of the organism and performance of sensitivity tests.

The urologist, by reason of the nature of his specialty, has long been impressed with the insidious nature of urinary tract infections in children, especially with the obvious deficit in clear-cut signs and symptoms which in the adult usually draw immediate attention to needed therapy. Under the circumstances members of this specialty may be pardoned for their evangelism, for it is apparent that many members of the medical profession are not cognizant of the fact that the recurrent cystitis of childhood may be the only evidence of obstructing congenital urethral valves, vesical neck contracture on a congenital basis, hydronephrosis or unilateral chronic pyelonephritis, any one of which, if left unrecognized, and therefore untreated, may lead to irreparable damage to the upper urinary tract. Whether the presenting symptoms are enuresis, bladder irritation, fever of undetermined etiology, or otherwise, all, no matter how insignificant, are deserving of careful investigation. Sometimes special techniques must be utilized to gain the desired information as to the underlying causative factor. Stewart, Bunge and others recently emphasized the value of the delayed cystogram in children for demonstrating reflux secondary to an incompetent ureterovesical junction as an important factor in recurrent urinary tract infection. The intravenous pyelogram may be modified by addition of oblique projection in the diagnosis of calculi with stasis and infection, a breathing film may be made in suspected perinephritis or perinephric abscess, or a delayed exposure in possible hydronephrosis. The cystometric examination coupled with careful neurologic survey may provide a clue in those instances in which disease of the upper or lower motor neuron has disturbed bladder function and made the patient more vulnerable to infection.

SUMMARY

It may be concluded that modern advances in the therapy of infectious processes has placed in the hands of the physician agents of inestimable value. The benefits to be received from them are directly proportional to the intelligence with which they are used. With few exceptions therapeutic failure in acute infections of the urinary tract may be traced to an inadequate approach to the problem. Once failure is evident, further investigation is mandatory, the alternative being irreversible chronicity.

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CHRONIC URINARY INFECTIONS IN INFANTS AND CHILDREN

GRAYSON CARROLL, M.D.

For clinical purposes we think of urinary infections in children as *acute, persistent,* and *recurrent.* The acute type we define as those which will subside under medication in a few days or a week. If, under the administration of the usual drugs, the infection continues, it may be termed persistent. This indicates that the drug given was not the proper one to inhibit the organism present. The recurrent type is that infection which clears up with proper medication, but after an interval the infection reappears. This indicates that the medication was correct, but there exists a pathologic condition which must be located and treated. Obstruction is the most common cause of recurrent infections.

This discussion will be confined to the persistent and recurrent phases, commonly called chronic.

THE PERSISTENT INFECTION

No one drug is available which will inhibit and kill all the organisms found in purulent urine, but certain drugs are more effective for certain organisms than for others. It is important, then, that we identify the organism and thereby know the behavior of this organism and what drug is most likely to inhibit it. We shall first approach this subject not so much from the standpoint of the location of the disease, although this too is important, but with the designation of the causative organism. This we believe to be necessary to proper understanding and treatment of urinary infections in children. For example, it is well to designate these diseases as *Bacillus coli* infection involving the bladder or Proteus infection involving the kidney, rather than merely cystitis or pyelitis.

From the Urological Service, St. John's Hospital, St. Louis.

As Welsh so aptly put it, "We are not so much fighting a disease as we are an organism."

URINE CULTURE

Since the identification of the organism is the important step in the treatment of persistent infections, care is taken in obtaining the urine for culture. This is done by the physician or a nurse trained in the method. We find it more difficult to do in children, requiring patience and persuasion. The male child's urine is collected by cleansing the meatus and, after the child has started urinating, passing the sterile container through the stream. In the infant often pressure or pinching the skin over the lower abdomen will provoke urination. The female child requires catheterization, best accomplished by a short metal catheter.

THE INFECTING ORGANISMS

Frequency of Occurrence. Campbell[2] makes an interesting observation that coccal infections predominate in the winter months as a result of the prevalence of respiratory infections at that season, and that bacillary infections are more frequent in the summer time because of the intestinal disorders such as dysentery in the warm seasons.

Anderson[1] recorded the frequency of occurrence of organisms found in 54 patients in pediatric general practice as follows: *E. coli,* 13; *Aerobacter aerogenes,* eight; Proteus, five; Paracolon, four; Pseudomonas, two; Staphylococcus, one.

Dr. Alison Garvan[4] at the Royal Alexandra Hospital for Children in Sydney, Australia, reported 382 patients with pyuria with the following frequency of occurrence: *E. coli,* 47 per cent; Staphylococcus, 23 per cent; Proteus, 12 per cent; Streptococcus, 5 per cent; Pyocyaneus, 3 per cent. The others were mixed infections.

Dr. Colston in 1932 reported that some 41 per cent of infections in children were coccal in origin, and Campbell[2] reported that 43.6 per cent of infections in children were coccal in origin.

The universal use of antibiotics has brought about marked changes in the flora of urinary infections in children. This is especially noted in hospitals and medical centers. This change is not so marked in the rural areas, where fewer antibiotics have been used. These detailed changes will be noted later.

It is apparent that the frequency of occurrence varies to such an extent that it is impossible to presuppose that one type of organism is present.

Characteristics. The behavior of an infection as observed in a child

will often suggest the organism involved before a cultural identification is available.

MICROCOCCAL (STAPHYLOCOCCAL) INFECTIONS

Pyelonephritis

The Micrococcus is frequently blood-borne from skin lesions, throat, tonsils, sinuses and respiratory infections.

The acute episode is characterized by fever, unilateral tenderness (if renal) with or without pus in the urine. Usually a positive culture is

Fig. 50.

Fig. 51.

Fig. 50. Multiple cortical abscesses caused by blood-borne Micrococcus.
Fig. 51. Portion of sclerotic kidney—end result of poorly treated pyelonephritis.

found. Although this is generally diagnosed as acute pyelitis, the pathologic picture is quite different (Fig. 50). Small cortical abscesses are first seen in the interstitial tissue, later coalescing to involve and destroy the tubules and glomeruli. This type of infection should be attacked vigorously and promptly because, if it is not successful, it will result in smoldering recurrences and scars with impaired function not detectable at the time, but leading to impaired renal function, renal rickets, hyperchloremic acidosis and chronic pyelonephritis in adult life (Fig. 51). Small narrow calyces and pelvis with a small kidney outline are typically observed in the pyelogram. Oddly enough, obstructive lesions are not observed in this type of disease (Fig. 52).

Perinephritic Abscess

The Micrococcus is characteristically the infecting organism in perinephritic abscess. Swan reported 32 cases at Children's and Infant's Hospital in Boston; the youngest was four months old.

Tenderness over the superior lumbar triangle, fever, chills, absence of the psoas shadow in the kidney, ureter and bladder film, may be treated as a Micrococcus infection immediately. Often the urine is negative, or only scant colonies of Staphylococci are present when the culture finally is reported.

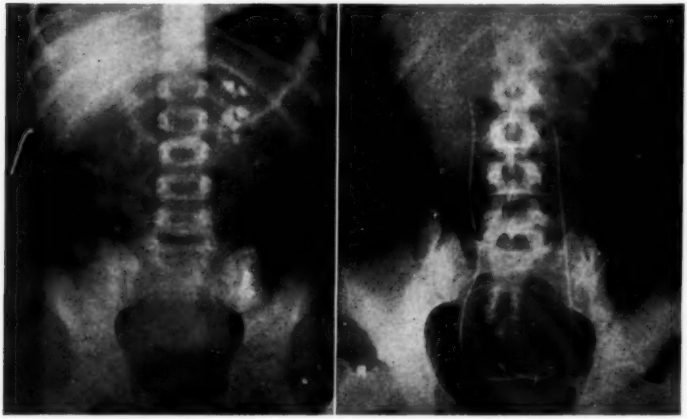

Fig. 52. Fig. 53.

Fig. 52. Ureteropyelogram of pyelonephritis showing narrow calyces from scarring. No obstruction noted.

Fig. 53. Perinephritic abscess. Abscess of psoas muscle shadow.

Immediate incision and drainage is not now always advisable, but watchful waiting to permit resolution under antibiotic therapy or a walling off in abscess formation before evacuation is done (Fig. 53) may be allowed.

Drugs of Choice in Micrococcal Infection

Penicillin is no longer the drug of choice in all coccal infections. In our survey at St. John's Hospital only 6 per cent of the Staphylococci were inhibited by penicillin. In the Massachusetts General Hospital only 26 per cent were sensitive to penicillin (Fig. 54). Reports coming from many other hospitals establish the fact that most of the Staphylococci causing urinary and respiratory infection are resistant to penicillin therapy. Erythromycin was effective in 80 per cent of our patients in St. John's Hospital and 97.5 per cent in Massachusetts General Hospital; Terramycin in 40 per cent. These latter drugs are rapidly becoming ineffective.

Unfortunately, erythromycin loses its effectiveness after it has been in use in a locality for four or five months. Probably "the best pro-

phylactic approach to drug resistance" may be multiple drug therapy as is observed in tuberculosis. Manten,[6] in reporting a carefully constituted study, states, "Erythromycin with streptomycin may be very potent since in vitro they usually are not only synergistic but also bactericidal." At present we use Ilotycin Pediatric, 1 teaspoonful three times daily and at bedtime. Pediatric drops may be used for infants. To reduce the probability of developing resistance one may give streptomycin solution, 0.5 cc. (approximately 200 mg.) intramuscularly once daily along with the erythromycin.

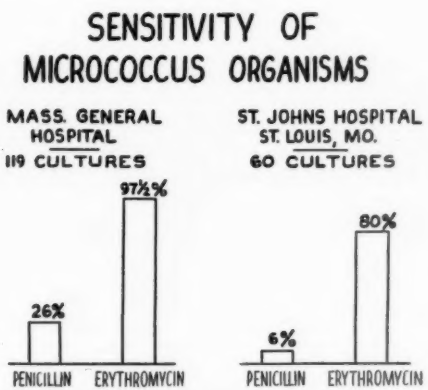

Fig. 54. Demonstrating the ineffectiveness of penicillin in this antibiotic period.

Terramycin is recommended when the organism is found to be sensitive. Terramycin oral drops, 100 mg. three or four times daily, are given in milk. The use of intramuscular Terramycin in children has been studied by Regan and Schwarzer,[8] who recommend an average of 400 mg. twice daily for children and 100 mg. twice daily for infants.

Penicillin, if given, should be in very large doses. The drug should be continued at least a week after the subsidence of infection, it being now well recognized that smoldering infections may not be eliminated in the kidney by short treatment.

ENTEROCOCCAL INFECTIONS

The Enterococcus, better known as *Streptococcus fecalis*, grows well on eosin-methylene blue agar; so it may be said that any coccal organism which grows well on this medium is probably Enterococcus. The Micrococcus does not.

May L. Porch[9] examined 100 strains of Streptococcus isolated from urine in children and found that 70 were *Streptococcus fecalis*.

This organism rarely forms abscesses. Its source is usually the intes-

tinal tract. It is quite resistant to many drugs and is best treated with Mandelamine or Terramycin.

PROTEUS INFECTIONS

This organism has a number of characteristics by which it can be suspected. Any urine which is persistently alkaline and by microscopic observation or smear is found to be a bacillus can be treated as a Proteus infection immediately, not waiting for the diagnosis by culture. The Proteus is often introduced by instrumentation or direct contamination from the feces, causing diaper rash in babies. It spreads into

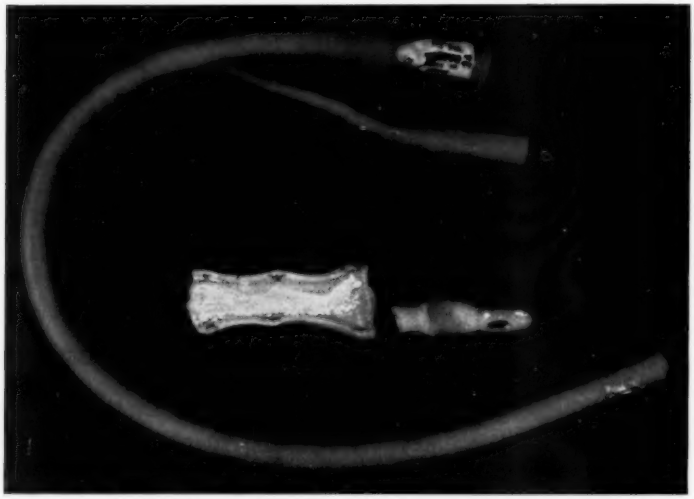

Fig. 55. Encrustations in indwelling catheter caused by Proteus infection.

the urethra and bladder and quickly into the kidneys, causing a continuous low grade infection rather than a violent episode. If encrustations or stones are present, all efforts at acidifying the urine will fail, but acidification can be accomplished by eliminating the Proteus.

The encrustations forming in a nephrostomy tube or catheter retained in the bladder are due to the Proteus organism, and prevention or eradication does not depend on acid diets and medication, but upon elimination of the Proteus (Fig. 55).

Treatment of Proteus Infections

Oxytetracycline, chlortetracycline, tetracycline, streptomycin and penicillin are not the drugs to use in Proteus infections.

Furadantin, Pediatric suspension, 1 teaspoonful four times daily, is the most satisfactory medication, if tolerated. Our laboratory has determined that an initial dose twice the usual dose produces an appreciable blood level therapeutically valuable. Drops in milk may be prescribed to babies who tolerate the drug very well. It can be given over a long period without ill effects and is excreted in large amounts in the urine. The prevention of chronic pyelonephritis and stone formation by giving Furadantin to rats in whose bladder the Proteus bacilli had been introduced is ample proof of the value of this drug in Proteus infections.

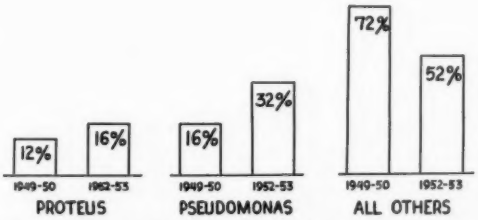

Fig. 56. The increase in the resistant bacilli (proteus and pseudomonas organisms) during the antibiotic era.

Gantrisin is another highly effective drug in Proteus infections. It is well tolerated and can be given over a long period also. One teaspoonful of Syrup of Gantrisin (0.5 gm.) may be given three or four times daily.

Chloromycetin (chloramphenicol) inhibits Proteus and should be used without question in severe infections. One teaspoonful of Suspension Chloromycetin Palmitate (125 mg.) is given three or four times daily. Chloromycetin can now be given intramuscularly once daily with a good blood level sustained for nine hours. The deaths reported from agranulocytosis were mostly those occurring from repeated doses, and recent figures indicate its rarity.

PSEUDOMONAS INFECTION

This infection exists in a small percentage of children. It most commonly occurs after instrumentation or contamination. Bacteremia following mastoid infections with subsequent urinary infection has been reported. This green-forming organism is cultured from feces and easily migrates to the urethra from diapers, bed clothing and night clothing from invisible fecal contamination, as does the Proteus.

Treatment of Pseudomonas Infection

This is the most resistant organism encountered. Of 67 strains isolated in our laboratory, only two were sensitive to any drugs other than

Polymyxin B. Recently we have discovered that the combination of streptomycin and oxytetracycline is highly effective, having controlled 49 of the 67 strains. One-half cubic centimeter (200 mg.) of streptomycin solution may be given intramuscularly once daily. Intramuscular Terramycin may be given to infants and children, in the dose range suggested by O'Regan and Schwarzer[8] in a study of 25 children. Infants may be given 200 to 400 mg. daily, and children an average of 700 mg. daily. Terramycin oral drops may be given, 100 mg. four times daily.

The Proteus and Pseudomonas are encountered more often in the last few years because of the many strains which have greater resistance to antibiotics.

These organisms comprised 28 per cent of the organisms found in 1949–50, but 48 per cent in 1952–53.

The clinician must know which is present, since their clinical behavior and response to drugs are different.

AEROBACTER AEROGENES

This organism is very similar to the *E. coli*, but it does not react the same to the antibiotics. It is found in about 7 per cent of the patients. The drug of choice in this condition is tetracycline. Achromycin Pediatric Drops (100 mg.) may be given three or four times daily.

Those drugs which so easily affect the Proteus and Pseudomonas do poorly with the Aerobacter.

NONSPECIFIC CHRONIC URETHRITIS

Chronic urethritis is common in infants and children. It is easily overlooked because it does not always give rise to fever, and the presence of a urethral discharge is not appreciated by the little patient or the doctor. A specimen withdrawn by the catheter may not show pus having bridged the urethra. Campbell[2] found urethrotrigonitis to be the most common cause of urinary infection in children and most commonly overlooked. Diapers, bedclothing from fecal contamination, and vaginitis are the common causes of recurrence. A small meatus in the male or female may go unnoticed. The voided specimen is cloudy from pus, the vagina margins and urethral meatus red, and a slight thin vaginal secretion present (Figs. 57 and 58).

B. coli, Proteus and Staphylococcus are most commonly found. If antibiotics have been used, fungus also is often observed on smear.

Untreated or poorly treated urethritis in a child results in strictured and sclerotic urethra, with polyps in the adult (Figs. 59 and 60).

Fig. 57.

Fig. 58.

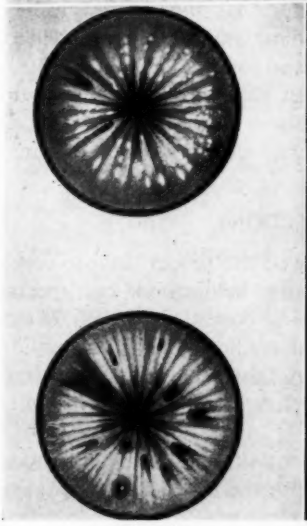

Fig. 59.

Fig. 60.

Fig. 57. Vaginitis causing urethritis in children.
Fig. 58. Pressure on the urethra causes the pus to appear.
Fig. 59. Periurethral glands chronically infected.
Fig. 60. Polyps of urethra, a result of chronic urethritis.

Treatment of Female Urethritis

Furacin suppositories are inserted in the urethra daily, if practical, and inserted in the vagina each night for a week. The antibiotic suited for the infecting organism is administered. Ointments of antibiotics are often irritating to the small child or infant and are not advised.

Dilatation of the urethra with a number 10 sound, gradually increasing to a number 20 French, is necessary for the resistant case.

One-half of a 0.5-mg. diethylstilbestrol suppository inserted in the vagina has proved successful in the intractable patient. This therapy was suggested by the article of Wilbur Lawson[5] and has proved helpful in the resistant case. This treatment of the vagina is important. Raymond Strept emphasized this and reports 15 children ranging from 26 months to 11 years having vaginitis as a source of recurrence of urethritis.

ENURESIS

Such emphasis has been put on the psychologic aspect of enuresis that the other probabilities have been discarded by many. The urologist recognizes many causes. Campbell[2] states that the greatest cause of enuresis is urethrotrigonitis, and dilatations and instillations will correct it. We use dilatations once weekly and sometimes Probanthine.

Harold McDonald reports having seen six children with interstitial cystitis. We have not seen this condition in such young patients, but it may have been overlooked and therefore deserves mention here.

RECURRENT INFECTIONS

This group comprises cases that received the proper drug to combat the causative organism, cleared up under medication, but recurred. This type of patient has some underlying condition, usually obstructive, which has not been detected and eradicated. No antibiotic or chemotherapeutic agent can cure this. A false sense of security is created by their continued use. The obstructive lesion must be found and eradicated.

Woodruff and Everett[11] studied patients in a follow-up for urinary infections at the Harriett Lane House with the initial infection ranging from seven months to 13 years. Most of those with mild febrile episodes without localizing symptoms and responding readily to treatment showed minimal renal damage. However, that group which had recurrent infections requiring hospitalization revealed definite evidence of urinary tract damage in the majority of cases. Lesions were found twice as often in those patients. The condition was usually found to be due to some anomaly or congenital or acquired obstruction which had not

been observed and relieved in earlier years. It emphasizes the necessity of complete examination of these children who have recurrent infections.

SUMMARY

Emphasis is given to (1) recognition and treatment of the infecting organism in infants and in children, and (2) the proper drug to be selected, often before the cultural differentiation of the organism is made, since most of the microorganisms have distinctive behavior patterns and can be surmised by the clinical course of the disease.

The persistent infections require identification of the organism and the selection of the proper drug of choice for that organism. The drugs of choice have been indicated.

The common finding of a vaginitis complicating a urethritis in female children is emphasized, and a treatment for its relief is suggested.

Emphasis is placed on the proper drug for the Proteus infection, and the combination of streptomycin and Terramycin for the treatment of Pseudomonas infections.

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KIDNEY TUBERCULOSIS IN CHILDREN

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Tuberculosis of the kidney is a serious complication of pulmonary tuberculosis, in children just as in adults. It tends to destroy the kidney, and it tends to be bilateral. It commonly causes no symptoms until the lesions are far advanced and refractory to therapy.

INCIDENCE

The percentage of incidence of renal tuberculosis among children, in 1955, is difficult to estimate. On the Pediatric Urological Service of the Squier Clinic at Babies Hospital, New York City, we have seen 22 children with positive urine cultures for *M. tuberculosis* in the past ten years. During this period there were 2063 new pediatric urologic admissions.

It is possible that we shall see a distinct lowering in the incidence of renal tuberculosis as a result of the use of the new antituberculosis drugs. As yet we have not been able to measure any conclusive decline. It should be noted, however, that in the past five years we have seen a tendency for a decline in the numbers of new cases of kidney tuberculosis in several hospitals (Fig. 61). No new cases with *M. tuberculosis* in the urine were discovered in the Babies Hospital in 1954, either among the miliary cases or the urologic cases (Fig. 61, bottom line). Some of this may be due to the usual lag in diagnosis, which is characteristic of this disease.

It is also possible, paradoxically, that we may see an increase in the incidence of renal tuberculosis, at some later date, as a result of the new antituberculosis drugs. More and more adults with pulmonary tuberculosis are now refusing to go to sanitoria. Instead, they go home

on ambulatory treatment with the new drugs. As their symptoms improve, some may neglect to keep up the dosage of their medications, thus reducing the effectiveness of their treatment. As a consequence, their sputums may become positive again, and they may spread tuberculosis among their children and among their contacts in the community, thus causing a later increase in renal tuberculosis.

	1950	1951	1952	1953	1954
V.A. Study	34	46	47	49	33
BRONX ONSET SX.	6	4	6	2	0
PRESBY. N.Y.C.	10	16	11	8	5
CHILDREN	1	3	2	1	0

Fig. 61. New cases of renal tuberculosis are still being diagnosed in numbers which show no conclusive decline in the incidence of this disease. The 1954 cases appear fewer, but the lag in diagnosis and reporting must be allowed for assaying these figures.

Fig. 62. Progression of renal tuberculosis in a child. (Roentgenograms courtesy of Dr. George F. Cahill.)

The seriousness of the disease, when untreated, is illustrated by the course of one of our pediatric patients who had had one kidney removed at age nine years, because of tuberculosis, and who was observed to have a tiny calcification in the papilla of the lowest calyx in the remaining kidney, at the time of nephrectomy. This calcification marked the site of the tuberculosis, which then went on to destroy the remaining kidney, causing death by uremia at age 19 (Fig. 62). Whether or not the disease is to become active in both kidneys is completely unpredictable, as is the rate of progression of any destructive lesion. Every patient with a positive urine culture for *M. tuberculosis*

must be treated with chemotherapy as if progression of the renal lesion was to be expected.

PATHOGENESIS

The pathogenesis of renal tuberculosis, according to Medlar,[3] is that of a hemic dissemination from the pulmonary or other primary lesion into the glomerular or cortical arterioles, where tiny caseous tubercles form.

MINIMAL (NONCAVITARY) RENAL LESIONS

This phenomenon occurs frequently during miliary disseminations in children. If such a blood-borne tubercle does not heal quickly, it may spill organisms down the nephron, and *M. tuberculosis* will appear in the urine at this time.

Minimal renal lesions (no pyelographic deformity) were present in 12 of our 22 children. Eight of these children had a positive urine culture during frank miliary dissemination, which caused the deaths of three of them, before the advent of chemotherapy. Urine cultures for *M. tuberculosis* in nine children have converted from positive to negative after long-term chemotherapy.

Medlar feels strongly that tubercle bacilli do not appear in the urine by "filtration" through an *intact* nephron. His studies have indicated that patients who have tubercle bacilli in the urine all have a sloughing renal lesion, however tiny, at that moment. He also feels that similar lesions are probably present in both kidneys because of the hemic dissemination. Such "minimal" tubercles, without pyelographic changes, may also occur in the kidney without massive miliary disease. They may follow primary pulmonary tuberculosis, and they were seen in 25 per cent of one group of patients who died of pulmonary tuberculosis at Bellevue Hospital. It should be noted, however, that not all these tiny lesions progress. Indeed, most of them heal spontaneously.

MODERATELY ADVANCED RENAL LESIONS

Moderate lesions (one cavity) were found in three patients, one of whom underwent nephrectomy, and two had the disease arrested by one year of "triple drug therapy" with streptomycin, sodium para-aminosalicylic acid and Isoniazid.

ADVANCED (DESTRUCTIVE) RENAL LESIONS

In some cases, however, the bacilli passing down the nephron from the tubercle in the glomerulus may stop in the region of the narrow

loop of Henle, causing a group of coalescing tubercles in the medulla. This area may caseate and slough out into a calyx, either on or beside the papilla of that pyramid. This will cause a small cavity in the medulla, which can be demonstrated by pyelography (Fig. 63). Once a cavity starts, it rarely heals spontaneously. Such a cavity usually grows larger, destroying the entire pyramid by caseation.

One of two possible courses may then be followed: First, the caseous contents of the pyramid may be retained, and a large, white caseous mass will remain, bulging against the renal capsule. This may calcify, leaving a large area of mortar-like material, replacing that pyramid. Or, second, the caseous contents of the pyramid can slough out, leaving

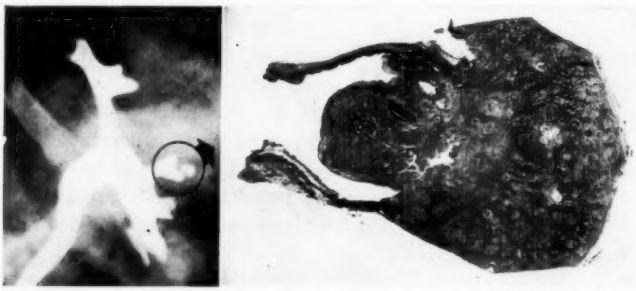

Fig. 63. An open tuberculous cavity (circle) forms in the papilla of the kidney when a caseous area sloughs out. This is the earliest roentgen sign of destructive tuberculosis of the kidney which can be detected. Once a cavity starts, it rarely heals spontaneously.

a ragged cavity, the margins of which are "moth-eaten" in a pattern easily recognized by the roentgenologist as diagnostic for tuberculosis. The disease may then spread to involve the entire pelvis and the linings of other calyces, with tuberculous granulations. Multiple blood-borne foci may start up in several pyramids at the same time. If, however, the disease is fairly well localized in only one or two pyramids, the walls of the empty cavities may then contract, causing indentations on the outer surfaces of the kidney to mark the site of the destroyed pyramids. These indentations are helpful to the surgeon who may be seeking to resect the involved portion of the kidney. He finds them, at the operating table, by stripping the renal capsule back and looking for the telltale indentations (or the bulging caseous areas).

Far advanced lesions were found in seven patients. Six had had one kidney removed. Two of these had severe bilateral renal lesions, and one of them died of uremia at age 19, before the days of chemotherapy. These two were the only patients who had demonstrable tuberculosis in both kidneys.

Three patients had their disease arrested by chemotherapy alone, and

four were cured by nephrectomy alone. One prostatic lesion became quiescent without chemotherapy.

Chemotherapy with multiple drugs for 12 months or longer has arrested the renal disease in all cases in which it has been used to date. One far advanced lesion was refractory to one year of streptomycin and para-aminosalicylic acid, but subsequently was arrested by one year of Isoniazid, streptomycin and para-aminosalicylic acid. Semi-bed rest, with bathroom privileges, is advised during the year of chemotherapy.

BONE TUBERCULOSIS

Bone tuberculosis was present in six of the 22 patients, and in four of the ten children who had definite (advanced) renal lesions. The hip was the site of the bone tuberculosis in three of the six children. The shoulder, foot and ankle were each involved in one additional patient. Four of the six patients were operated upon one to three years prior to a diagnosis of genitourinary tuberculosis. Of the remaining two patients, bone tuberculosis developed in one in the same year during which urinary tuberculosis was diagnosed. The last patient had tuberculous bursitis of the shoulder four years after nephrectomy. In some patients, pyuria was found at the time of the osseous tuberculosis and led to the diagnosis of kidney tuberculosis.

Bladder and Genital Lesions

If the disease is allowed to continue its natural course, the organisms spilling down the ureter will infect the walls of the ureter, causing strictures and irregularities. The bladder may eventually be infected, with red areas appearing around the ureteral orifices and on the trigone. Isolated bladder ulcers may form in patches, on the bladder wall. The ultimate complication may be contracture of the urinary bladder due to fibrosis throughout the wall, causing disabling urinary frequency and dysuria. Fortunately, in children, this complication rarely has time to develop before the disease is detected. In males the bacilli may drop into the prostatic ducts, infecting the prostate gland and later descending the ductus deferens to infect the epididymis.

The time intervals involved between the known pulmonary primary lesion and the development of pyuria and visible destructive lesions of the kidney may be of the magnitude of three to 20 years. On the other hand, moderate pyuria (four to six white blood cells per high power field) and positive urine cultures for *M. tuberculosis* frequently occur within a few days or weeks after a miliary dissemination, due to blood-borne tubercles in the glomeruli, which may then heal spontaneously.

If the urine cultures are positive and a cavity is demonstrable by roentgenogram, the lesion is older, and will be much more difficult to control by chemotherapy alone than if there are no roentgen (cavitary) changes.

The primary tuberculous lesions in these children were usually in the lungs. Among the 22 children with kidney tuberculosis studied here, 16 had definite pulmonary lesions by roentgenogram, most of which were healed. Two others had no detectable sign of pulmonary tuberculosis, either healed or active, although one of these had a tuberculous hip. One child had tuberculous cervical lymph nodes to mark the probable portal of entry of the disease. Eight other patients had miliary tuberculosis, visible in the chest film. All eight of these children had positive urine cultures at the time of the miliary disease in the chest. Three had high sedimentation rates (over 47 mm. in one hour), attributable to their miliary disease rather than their renal lesions. Seven had many white blood cells in the urine at that time. The remaining child had no pus cells in the urine even though the urine culture was positive. In one child the miliary dissemination may have arisen from an advanced kidney lesion.

The "contact" from whom these patients had presumably caught their tuberculosis was unknown in four and known in 18 of the 22 patients, most of whom were exposed to persons with open pulmonary tuberculosis in their own household. The size of the tuberculous kidney lesion was small ("minimal"), with no roentgen changes, in 34 of the 44 kidneys. It was "moderately advanced" (one calyx involved) in three kidneys and "far advanced" (two or more calyces involved) in seven kidneys.

The amount of pyuria was slight (none to five white blood cells per high power field) in 11 patients, moderate (five to ten white blood cells per high power field) in five patients, and heavy in six patients. Pyuria decreased sharply or disappeared, after treatment, in all but the two bilateral "advanced" cases.

The erythrocyte sedimentation rate was normal in seven patients, between 20 and 30 mm. of mercury in two patients, elevated over 30 mm. in seven patients, and unknown in one, at the time when the disease was diagnosed. The sedimentation rate fluctuated in an unpredictable manner before the treatment was started, but fell towards normal after chemotherapy or nephrectomy. The erythrocyte sedimentation rate was elevated in most of the patients who had miliary tuberculosis, and in all six patients with bone tuberculosis. In those whose only active lesions were in the kidneys it was not elevated, suggesting that, as in adults, renal tuberculosis does not usually cause an elevation of the erythrocyte sedimentation rate.

Genital tuberculosis was rare in these children. It occurred, as bilat-

eral epididymitis, at the age of two years, in only one out of the nine male patients. After bilateral epididymectomy the presumptive prostatic lesion in this child apparently underwent spontaneous arrest.

Bladder involvement was severe in seven patients, mild in three, and absent in four patients. In eight it was unknown, since they (the miliary cases) had no cystoscopy. All seven patients with far advanced renal lesions had extensive cystitis, which responded satisfactorily to chemotherapy. No child suffered a contracted bladder. A pink and white dotted effect was often noted on the trigones of these patients with renal tuberculosis, which persisted even after the disease was quiescent. This made the trigone stand out brightly when viewed through the cystoscope, and was due to a maze of tiny dilated vessels on a pale background.

The first genitourinary symptom was dysuria in eight of the 22 patients. Pyuria was found accidentally, while the patient was being investigated for other reasons, in four more patients. Tubercle bacilli were grown from urine cultures taken routinely on eight patients with miliary tuberculosis. Among the eight patients who had dysuria there were two who had mild, dull pain in the kidney region, and one who had gross hematuria. Five patients had no symptoms, despite pyurias of three to five white blood cells per high power field or over.

There were four deaths among the 22 children. Three died of generalized tuberculosis, following miliary disseminations, before the days of chemotherapy. These children did not die of uremia, even though the kidneys contained tiny tubercles. There was one child, mentioned earlier, who did die of uremia, at age 19. Her right kidney had been removed at age nine years, at which time a tiny calcification in the other kidney marked the site of the disease, which subsequently destroyed her remaining kidney (see Fig. 62).

The time interval between the known pulmonary infection and the diagnosis of destructive (cavitary) renal tuberculosis ranged from two months to four years in this series. The patients with miliary lung lesions had positive urine cultures during the miliary dissemination.

TREATMENT

For treatment purposes it is our current practice to classify children with *M. tuberculosis* into two groups: those with minimal lesions (no pyelographic deformity) and those with advanced lesions (one or more excavated calyces).

Chemotherapeutic Regimens

Minimal Lesions. Start on triple drug therapy with streptomycin, 20 mg. per kilogram of body weight in a single injection, twice weekly;

Isoniazid, 5 mg. per kilogram per day, in three divided doses; and para-aminosalicylic acid, 6 to 12 gm. per day, in three divided doses. After six months the streptomycin may be discontinued, and the Isoniazid and sodium para-aminosalicylic acid continued for a total of one year. In obvious miliary cases both the streptomycin and the Isoniazid may be curtailed.

Advanced Lesions. Patients with advanced lesions should receive triple drug therapy as for minimal lesions for 12 to 18 months.

Genital Lesions. Genital lesions are treated with the same regimen as for advanced lesions.

Preoperative Chemotherapy

If one kidney is severely destroyed and the other appears normal, it may sometimes be desirable to remove the destroyed kidney under the protection of chemotherapy. In these cases it is our present practice to give Isoniazid and para-aminosalicylic acid (dosage as for minimal lesions) for one to four months preoperatively, and to continue post-operatively for a total of one year. In this way we hope to reduce the chances of dissemination, and to heal any tiny tubercles which may be present in the contralateral "good" kidney.

Results

Three patients with destructive (advanced) renal lesions, visible by pyelography, were treated with triple drug therapy. No operation was done. Streptomycin, sodium para-aminosalicylic acid and Isoniazid were administered for one continuous year, and the urine examinations of all three patients have now remained negative for two years. Two other patients received streptomycin and sodium para-aminosalicylic acid for one year and also had negative results of urine examination.

These preliminary results compare favorably with those obtained by nephrectomy in seven patients, in two of whom destructive tuberculosis developed in the solitary remaining kidney. One of these two died of uremia (before streptomycin), and the other had the disease later arrested by two years of combined chemotherapy.

Miliary cases, with positive urine cultures (and no destructive renal lesions by roentgenogram), were treated by a different chemotherapeutic regimen by Drs. Damrosch and Alexander of our miliary study group. They receive more intensive streptomycin, Isoniazid or Promizole treatment for 12 weeks, plus para-aminosalicylic acid. If the response was satisfactory, only the para-aminosalicylic acid was kept up for another six to 12 months. It was presumed that the renal lesions in these cases were tiny tubercles of the type which usually heal spontaneously even

without chemotherapy. Three other patients had neither nephrectomy nor chemotherapy, in the years before streptomycin. Two of these three died of disseminated tuberculosis. The other appeared to have undergone spontaneous arrest of the kidney lesion, which was small. All the "minimal" renal lesions, which were too tiny to cause any roentgen change, were arrested by one year of chemotherapy with either two or three of the afore-mentioned drugs.

The only failure from chemotherapy occurred in a patient with a far advanced lesion, treated with only two drugs (streptomycin and para-aminosalicylic acid) for one year. The disease was then arrested by triple drug therapy.

Though this series is small and the follow-up is short, the results parallel those found in our larger experience with chemotherapy in adults.

SUMMARY

Mortality from bilateral renal tuberculosis has dropped from 80 down to 8 per cent, in our current study. Triple drug chemotherapy appears so effective, in preliminary surveys, that all nephrectomies are currently being deferred indefinitely at this treatment center. Whether chemotherapy will ever replace excisional therapy for genitourinary tuberculosis is problematical, but it certainly has greatly enhanced the outlook for patients with this once lethal disease.

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NEUROMUSCULAR DISEASE OF THE URINARY TRACT IN INFANTS AND CHILDREN

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The diagnostic problem of neuromuscular disease of the urinary tract in children always has been one chiefly of differentiation from the obstructive uropathies. Advanced degrees of ureteropyelectasis in infants or children in whom definite obstructive lesions can be found, such as congenital valves of the urethra or stenosis of the urethral meatus, present little diagnostic difficulty. Likewise patients who have unmistakable signs of congenital disease of the central nervous system (nearly always myelodysplasia) are easily evaluated. It is the large group of "borderline" patients who present the difficult problems in diagnosis as well as treatment. For ease in discussion of this poorly defined subject we have arbitrarily divided the subject into two parts, namely, (1) nonobstructive ureterectasis and (2) vesical dysfunction caused by myelodysplasia.

NONOBSTRUCTIVE URETERECTASIS

Etiology

The problem posed by ureterectasis always has been one of etiology. Is it obstructive? If so, where is the obstruction? Is it "primary" disease of the ureter, such as atony or neurogenic or neuromuscular disease? If so, what type of lesion is responsible? The first job of the urologist is to exclude obvious obstructive lesions, such as stone, stric-

ture, tumor, ureterocele and vesical diverticula obstructing the ureter. If none of these classic varieties of obstruction can be demonstrated, then what to do? Much has been written about narrowing of the intramural portion of the ureter and the therapeutic results achieved by repeated dilatation or meatotomy or both. By what standards can one judge this factor? This portion of the ureter appears narrow in any normal ureterogram. If a number 5 or 6 French ureteral catheter will pass through the ureter at this point in a child, can one state that a definite obstruction exists? Is further dilatation with instruments as large as number 10 or 12 French catheters or bulbs therapeutic or traumatic? The answer, of course, is not clear, but we suspect that many normal intramural ureters have been subjected to traumatic and ineffectual dilatation for obstruction that did not exist.

Attempts have been made to classify the nonobstructive types of ureterectasis into (1) those associated with a normal ureteral orifice and intramural ureter, with no reflux, and (2) those associated with a dilated orifice and intramural ureter, with reflux. The former types have been called "congenital hydroureter" or "hydroureter," whereas the latter have been termed "megaloureter." From a urographic viewpoint the classification is of interest, but is of little or no help in determining the causative factor or in planning treatment.

Achalasia of Ureterovesical Junction. Many theories have been advanced to explain nonobstructive ureterectasis. One of the most widely accepted is that of achalasia of the ureterovesical junction; this suggests disturbance of the normal physiologic action of the intramural portion of the ureter, which produces "relaxation" as the urine passes downward into the bladder, but produces "contraction" or a valvelike action, preventing regurgitation of urine from the bladder back into the ureter, when the detrusor urinae contracts. If such a situation does exist, we have not learned to recognize it accurately or to treat it adequately. Therapeutie attempts, such as dilatation, meatotomy or reimplantation of the ureter into the bladder, as well as plastic procedures on dilated, tortuous ureters to eliminate redundancy and excessive dilatation, have not been uniformly successful.

Primary Atony of the Ureter. Primary atony of the ureter caused by inflammation or neurogenic or neuromuscular disease has been a common diagnosis. The disconcerting fact in such cases is that most dilated ureters have thick muscular walls and are not thinned-out tubes, as one would expect with atony. To account for this finding, it has been suggested that the condition represents a congenital persistence of the dilated fetal type of ureter.

Congenital Defect in Innervation. Congenital defect in innervation of the ureter has been suggested. It is pointed out that the dilated, thickened ureter may be compared to the trabeculated and thickened de-

trusor seen in a nonreflex cord bladder whose nerve connections to the spinal cord have been severed. The weakness of this theory lies in the fact that, whereas the vesical lesion can be reproduced experimentally by section of nerves or spinal cord, the ureteral abnormality has not been reproduced. Furthermore, no type of nerve section ever has produced therapeutic results in ureteral dysfunction.

Hypertrophy of the Ureter. Probably the most attractive and plausible theory suggests that the dilated, thick-walled, tortuous ureter results from hypertrophy of the ureter working against back pressure, most likely transmitted from the bladder. This appears especially likely in the megaloureter in which *vesico-ureteral reflux* is present.*

Ureteral Reflux. This is an exceedingly interesting and poorly understood phenomenon present in a large percentage of cases of ureterectasis. Just what part does it play and what light does it throw on this difficult problem? As intimated earlier, the physiologic mechanism of the ureterovesical junction is poorly understood. In 1928 and 1929 Gruber[21, 22] showed that the excised human bladder can be distended to the point of rupture without reflux of fluid up the ureters. Clinical experience has demonstrated that atonic, decompensated, thinned-out bladders resulting from either long-standing obstruction of the vesical neck or lesions involving the afferent nerve pathways, as in a tabetic cord bladder, almost never show reflux or ureterectasis. On the other hand, compensated trabeculated bladders with thickened powerful detrusors, such as are found in both simple obstruction of the vesical neck and the nonreflex type of cord bladder, often are associated with ureteral reflux and ureterectasis.

The statement made years ago by Graves and Davidoff[18, 19] concerning the cause of reflux still appears to be the most logical explanation yet advanced. They stated that reflux results from "sustained tonus of the bladder musculature as it actively resists distention." This statement intimates that it is not increased intravesical pressure alone that produces reflux, but rather an additional factor of distortion or weakening of the ureteral orifice and intramural ureter as a result of the unphysiologic situation that arises from contraction of the bladder when the vesical outlet is obstructed or will not relax in normal fashion (reciprocal action of the detrusor and vesical neck).

In our opinion, this accurately describes the situation found in the usual cord bladder, in which one of the commonest findings is an "ina-

* Campbell[3] expressed the opinion that back pressure, even in the absence of reflux, can be a potent factor in the production of ureterectasis. In discussing the obtuse angle formed by the junction of the normal-appearing intramural ureter and the dilated ureter above, as found in so-called congenital hydroureter without reflux, he accredited prolonged back pressure, probably originating in fetal life, as the cause of the ureteral dilatation and elongation. He considered that this angulation then becomes a secondary obstructive factor.

bility to accommodate readily and easily to increasing increments of fluid (distention)."[6] Hutch[23] recently called attention to an additional factor in reflux. He noted the frequency of "saccules," or small vesical diverticula, adjacent to ureteral orifices, especially in cord bladders with reflux. Also, he demonstrated that in most cases the ureter lies in the wall or floor of this diverticulum, so that the normal muscular wall or "floor" of the intramural ureter is weakened or entirely missing. Theorizing that the intravesical pressure of fluid exerted against the firm muscular "floor" of the intramural ureter during micturition is an important factor in the valvelike action (which prevents reflux in normal persons), he thought that loss of this firm muscular floor caused by these diverticula may be important in the production of reflux.

The explanations of reflux just given lend weight to the hypothesis that many instances of nonobstructive ureterectasis may be the result of some type of vesical dysfunction, either simple mechanical obstruction of the vesical neck or neurogenic dysfunction. Recent observations of Swenson and associates[26–30] further support the view that the bladder should be suspected more often as the cause of unexplained nonobstructive ureterectasis. These workers have postulated that the cause of Hirschsprung's disease (congenital megacolon) is absence of peristalsis in the rectosigmoid caused by absence of parasympathetic ganglionic cells (Auerbach's plexus) in this portion of the intestine. This inactive terminal portion of the intestine acts as an obstruction, causing dilatation of the proximal portion, which is unable to overcome the obstruction even though its muscular walls become greatly hypertrophied by overwork.

Further extending their observations to children with megaloureters, they considered that they have been able to demonstrate either absence of or great reduction in the number of ganglionic cells normally present in the adventitia of the bladder in the region of the ureteral orifices. They called attention to the often-overlooked associated vesical dysfunction in these cases, manifested by such conditions as an abnormally large bladder, residual urine and abnormalities in the cystometrogram. They concluded that megaloureters are often the result of an abnormal bladder rather than of a primary lesion of the ureters and suggested, as treatment, prolonged drainage of the bladder by suprapubic cystostomy.

Summary. It is obvious that the problem of nonobstructive ureterectasis is far from being solved. However, from available evidence, one gains the impression that in many cases it may be the inefficient or unsuccessful attempt of the bladder to empty itself or its resistance to overdistention (whether due to an obstructed outlet or faulty innervation) or a combination of these factors that is the inciting agent in the production of both ureterectasis and reflux. At present, therefore, it

appears that the practical approach to this obscure condition would be first to exclude with care any obstructive lesion in the course of the ureter, including the ureterovesical juncture and ureteral orifice. If none is found, attention should be directed to the bladder.

VESICAL DYSFUNCTION FROM MYELODYSPLASIA (SPINA BIFIDA)

Myelodysplasia (spina bifida) is a congenital defect of the spinal column that results from failure of fusion of the dorsal walls of the primitive neural canal. It is nearly always situated dorsad and nearly always located in the lumbosacral region. The lesion may be of such a mild degree that there are no symptoms or neurologic findings. In an occasional patient, signs and symptoms may appear only as the child becomes older and growth puts more strain on the defective nerve roots.

The degree of disability caused by myelodysplasia is dependent on the extent of the defect and the amount of degeneration of or damage to the spinal cord, nerve roots and cauda equina. Because this condition usually affects the lumbosacral portion of the spinal cord and the cauda equina, the reflex center for micturition usually is involved. Therefore the lesion would be referred to as a nuclear or infranuclear lesion,[7] and one would expect the neurogenic vesical dysfunction more or less to follow the pattern of the autonomous or nonreflex cord bladder caused by acquired lesions of the lumbosacral part of the spinal cord or the cauda equina or both.[8]

The principal findings in myelodysplasia include impairment or absence of sensation in the perineal region (saddle area) and lower extremities, motor weakness (flaccid) of the perineum and lower extremities, absence of reflexes and varying degrees of muscular atrophy of the lower extremities. In addition, there may be loss of rectal sphincteric tone with fecal incontinence, vesical dysfunction, consisting in retention and incontinence, and other congenital anomalies, principally clubfoot.

Mention has already been made of the possibility of delay in appearance of signs and symptoms. Even though the spinal cord may be well developed, the nerve roots may have been damaged as they pass through abnormal mesodermal tissue, so that findings may not appear until later in life, when growth, stretching of the nerves or other factors may make the abnormality apparent. Langworthy and associates[24] stressed this fact in relation to vesical dysfunction that appears only as children become older, the implication being that possibly some lesions diagnosed as simple congenital obstruction of the vesical neck in reality may be instances of mild myelodysplasia in which other symptoms or findings are not apparent. This point should be remembered later when

we consider the differential diagnosis between myelodysplasia and "simple" congenital obstruction of the vesical neck as causes of vesical dysfunction.

Theoretic Aspects

As previously indicated, the type of vesical dysfunction one would expect in myelodysplasia should simulate the autonomous, or nonreflex, cord bladder, the typical findings of which are (1) thickened detrusor and trabeculation, (2) inefficient emptying with substantial amounts of residual urine and (3) "active"[9] incontinence with frequent, irregular spurts of varying amounts of urine. Also, because of the great variation in severity and completeness of the neurologic lesion, one would expect a wide range of variation in the degree of vesical dysfunction, which is exactly what is found clinically. Another factor that must be taken into consideration is the relative degree of involvement of the sensory (afferent) and motor (efferent) components of the reflex arc for micturition. Although it is difficult to imagine only the sensory or only the motor fibers being involved, we do see cases in which involvement of one or the other appears to be more important. Predominantly sensory involvement should tend to simulate the atonic bladder of tabes,[11, 12] while predominantly motor involvement or equal amounts of motor and sensory involvement should produce the typical trabeculated autonomous nonreflex type of bladder just described. Attempts have been made with questionable success to distinguish the relative involvement of the two components by means of cystometry.[24]

If this were the entire story, the treatment of vesical dysfunction in myelodysplasia could be reasonably successful, but another factor is concerned that only too often defeats therapy. This is the apparent involvement of the pudendal nerve fibers (somatic), which supply the voluntary muscles of the perineum, including the external sphincter. This flaccid incompetence of the external sphincter (rarely seen in acquired lesions* of the spinal cord)[10, 17] allows varying degrees of "passive" incontinence, for which to date little if any successful treatment is available.

Practical Aspects

From a practical standpoint there are four outstanding problems to be considered, namely, (1) urinary incontinence, (2) inability to empty the bladder completely (residual urine), (3) associated ureterectasis, reflux, infection and renal insufficiency, and (4) rectal incontinence.

* In most acquired lesions of the spinal cord the tonicity of the external sphincter is normal or increased.

Because of the great differences in degree of damage to the spinal cord and nerves, one sees a tremendous variation in the severity of vesical symptoms from patient to patient. For instance, one patient may have minimal disturbances, consisting of mild obstructive urinary symptoms with a minimal amount of residual urine and no leakage, but with recurring episodes of urinary infection and fever. Another patient may suffer from continuous urinary incontinence, severe infection, residual

TABLE 9. *Comparison of Symptoms and Findings in Congenital Obstruction of Vesical Neck and Myelodysplasia*

SYMPTOMS AND FINDINGS	CONGENITAL OBSTRUCTION (105 CASES)	MYELODYSPLASIA (53 CASES)
Fecal incontinence	None	About half
Urinary incontinence (day and night)	Less than a third (30)	All
Enuresis only	A fourth	None
Residual urine:		
Less than 30 cc.	Less than a third (30)	Almost none (3)
30 to 100 cc.	A fifth (20)	A third (16)
More than 100 cc.	More than half (55)	Two thirds (34)
Infected urine	85 per cent	85 per cent
"Recurring infection"	Three fourths (76)	Less than half (21)
"Obstructive" symptoms: Poor stream, difficulty in voiding	A fifth	A fifth
Increase of blood urea	A third (32)	A fourth (13)
Gastrointestinal symptoms only (from azotemia)	7	None

urine, pronounced dilatation and reflux of the upper part of the urinary tract, renal insufficiency and rectal incontinence. The latter patient is a social outcast because of the constant odor of ammoniacal urine and feces.

Differential Diagnosis between Vesical Dysfunction of Myelodysplasia and That of Congenital Obstruction of the Vesical Neck. In a review[15] of our experience at the Mayo Clinic with transurethral resection of the vesical neck in infants and children over a period of 19 years (1934–1952, inclusive) we divided the 158 cases studied into two groups, namely, simple congenital obstruction of the vesical neck (105 cases) and myelodysplasia (53 cases). As a general rule it was not difficult to make this division, since only an occasional case appeared to be ques-

tionable or borderline. Evidence of the presence of myelodysplasia was furnished chiefly by the following data: (1) roentgenologic evidence of spina bifida or deformity of the sacrum (not pathognomonic, however, because at least a third of routine roentgenograms of the lumbar portion of the spinal column of normal persons show this defect); (2) sensory changes in the saddle area and lower extremities; (3) motor changes in the perineum and lower extremities; (4) vesical incontinence; (5) rectal incontinence; and (6) clubfoot or other associated congenital anomalies. Comparison of the symptoms and findings in these two groups of cases as listed in Table 9 is illuminating. It may be of help to the reader in deciding whether he is willing to accept the two groups as indicative of lesions of entirely different cause or would rather subscribe to the view that both groups are variations of myelodysplasia. We are inclined to support the former view.

The Therapeutic Problem

One recognizes three main objectives in treatment as follows: (1) Elimination of residual urine. This is important in order to be able to eliminate the infection, relieve the renal insufficiency and protect the upper part of the urinary tract by relief of the ureterectasis and reflux. By restoration of more nearly normal renal function, the child will be permitted to grow and develop normally. (2) Elimination or reduction of the degree of urinary incontinence so that the patient may be kept dry and without objectionable odor. As already mentioned, this often is impossible in these patients because of the "passive"[9] incontinence resulting from hypotonicity of the perineal muscles and external urethral sphincter peculiar to this disease. (3) Control of fecal incontinence.

"Conservative" treatment consists chiefly in teaching the patient to use abdominal straining or manual expression (Credé) or both to empty the bladder, or the use of intermittent catheterization or an indwelling catheter. Because the situation is one of an autonomous, nonreflex type of neurogenic bladder, fairly complete emptying often may be obtained by teaching the patient to void at regular intervals, straining with the abdominal muscles and diaphragm, together with use of manual compression over the lower part of the abdomen. If the bladder can be emptied fairly well in this manner and if there is minimal or no flaccid involvement of the external urethral sphincter and perineal muscles, the patient may stay dry for substantial periods between evacuations of the bladder. If such a procedure is unsuccessful, intermittent catheterization every four to six hours may be sufficient to keep the patient dry and comfortable. In some cases such a regimen has been carried out for years with a minimum of serious complications; modern

urinary antiseptics have greatly assisted in this form of treatment. However, if the patient does not remain dry between catheterizations, an indwelling catheter may be used. Patients ordinarily will not tolerate an indwelling urethral catheter for long periods (months or years), so that this treatment is not too practical. Suprapubic drainage likewise is not satisfactory because the patient may continue to leak through the urethra in spite of it.

Moderate success has been obtained in some instances by means of operation on the vesical neck, chiefly transurethral resection. The problem is similar to that of the autonomous (nonreflex) cord bladder resulting from nuclear or infranuclear transection of the cord. One can predict with reasonable accuracy whether or not transurethral resection will be effective by observing the patient after complete evacuation of the bladder by catheterization. If a substantial amount of residual urine is present and if the patient remains dry after catheterization for one hour or more, it indicates that the malfunctioning vesical neck is acting as an obstruction and that the external urethral sphincter is probably intact. In such instances adequate transurethral resection, done in multiple stages if necessary,[13, 14] should allow the patient to empty the bladder completely with or without use of abdominal straining and manual compression.[16] Usually this will eliminate all leakage. In most such patients the elimination of residual urine also reduces the ureterectasis, relieves the back pressure on the kidneys and allows renal function to return to normal or near normal.

In some patients, however, in whom vesico-ureteral reflux of severe degree is present, damage to the upper part of the urinary tract may progress, apparently because of the intermittent back pressure from reflux that occurs during voiding. Compromise of the lower portions of the ureters by adjacent small congenital vesical diverticula may prove to be an additional complicating factor. Often the ureteral orifices (single or duplicated) may open on the edge of or just inside such diverticula. As mentioned previously, Hutch[23] has shown that in most instances the ureter courses just under these diverticula so that there is no longer any muscular support of the "floor" of the intramural ureter against which compression may be exerted by intravesical pressure to accomplish the normal valvelike action that prevents reflux. In Hutch's experience this is a common occurrence in cord bladder with ureteral reflux. He described an operation for this condition that consists in dissecting free the intramural ureter, being careful not to detach its terminal portion from the trigone. The bladder is then reconstructed under the intravesical ureter so that the diverticulum is obliterated, with restoration of a firm muscular "floor" against which compression from intravesical pressure may be exerted.

A case which illustrates these complicating factors is presented.

CASE REPORT. A 10 year old girl was admitted to the Clinic in November, 1947, for urologic evaluation. The past history revealed many episodes of serious febrile illness, associated with urinary infection, large amounts of residual urine and pronounced dilatation of the upper part of the urinary tract with renal insufficiency. There had been difficulty with rectal control. When the child was 5 years of age, the mother had been advised by her physician to catheterize the child 4 times daily. For 5 years this treatment had been carried out, the child rarely if ever making any effort to void. There was no leakage of urine with this regimen. The use of a constipating diet and enemas every third day had kept the bowel situation well under control, so that the patient rarely if ever soiled herself.

Fig. 64. Preoperative excretory urogram made in November, 1947.

Neurologic examination at the Clinic revealed some diminution in the sensation of touch in the perianal region. The tone of the rectal sphincter was greatly reduced. A plain roentgenogram showed spina bifida occulta. A neurologic diagnosis was made of myelodysplasia.

An excretory urogram (Fig. 64) demonstrated bilateral duplication that was incomplete on the right (one ureteral orifice) and complete on the left (two ureteral orifices). Both pelves on the right showed minimal pyelectasis, grade 1, graded on the basis of 1 to 4. On the left side the upper pelvis was almost normal; the lower segment showed no function in the 5- and 20-minute films (no later film was made). A retrograde cystogram showed no reflux, but neither a delayed nor a voiding film was made. The bladder was pyramidal in shape and greatly trabeculated. The patient was allowed to go all day without catheterization. Several times she tried to void, but this was accompanied by great difficulty and straining, and only small amounts of urine were voided. A check of residual urine at the end of this time showed more than 300 cc. of urine present. Cystoscopy revealed an extremely trabeculated bladder; it was difficult to determine whether or not the vesical neck was abnormal in appearance. Two small congenital diverticula were symmetrically placed, one on either side of the bladder in about the position where ureteral orifices normally should be found. The single ureteral orifice on the right was situated just on the medial edge of the right diverticulum. On the left side the ureteral orifice serving the upper pelvis was located on the medial edge of the diverticulum. The one serving the lower pelvis was situated deep inside the diverticulum on its medial wall, and it showed a mild degree of gaping.

Treatment consisted in transurethral resection of the vesical neck in two stages, using the Thompson infant (18 French) punch resectoscope. The entire circumference of the vesical neck was resected. At the first sitting 25 pieces of tissue were removed. The patient voided poorly after the first operation, so that a second resection was done, with removal of 40 pieces of tissue. After this procedure the patient was able to void easily and normally, with perfect urinary control; the bladder emptied completely and no residual urine was present. The patient was allowed to return home. Examination at home during several succeeding months showed absence of residual urine.

The patient returned in January, 1949 (1 year after operation), because of diffi-

culty in voiding for the preceding 2 months. An excretory urogram showed some increase in the degree of dilatation of both pelves of the right kidney; poor function and pyelectasis were still present in the lower segment of the left kidney. A retrograde cystogram showed reflux up all ureters, outlining all 4 pelves (Fig. 65). Both pelves on the right were moderately dilated. On the left the upper pelvis was dilated, grade 1, and the lower, grade 3+. Residual urine measured 100 cc. Passage of urethral sounds and administration of urinary antiseptics relieved the symptoms, and the patient was allowed to return home.

The patient did not return to the Clinic until 1954 (6½ years after operation), and then she came only for a checkup. Since her last visit she had been well and had had

Fig. 65.

Fig. 66.

Fig. 65. Retrograde cystogram made in January, 1949, showing reflux up all ureters, with outlining of all 4 pelves.

Fig. 66. Excretory urogram (210-minute film) made in July, 1954. All pelves, including the left lower pelvis, are outlined.

no urinary difficulty. She voided easily, had good control and had no nocturia. Urinalysis showed a grossly clear urine, but microscopic study of a centrifuged specimen showed 25 pus cells per high power field. There was no residual urine.

An excretory urogram (Fig. 66) revealed definite increase in the degree of dilatation of the two pelves on the right side. On the left the upper pelvis was still only slightly dilated, and a 3-hour film outlined the lower pelvis, which was still greatly dilated, although the exact degree could not be determined because of incomplete filling. A retrograde cystogram revealed reflux up the ureter serving the lower pelvis of the left kidney. We were considerably concerned over the apparent increase in degree of ureteropyelectasis and thought that it was no doubt on the basis of back pressure from reflux. The vesical diverticula also were considered complicating factors, possibly contributing to the ureteral obstruction and reflux. On the assumption that the amount of back pressure in the ureters during voiding might be reduced if the vesical neck were further weakened, another transurethral resection of the vesical neck was done. As the patient was now 16 years of age, the urethra was of adult size; so the size 24 French Thompson punch resectoscope was used. A total of 3 gm. of tissue was

removed. After operation the patient voided normally, as she had done before operation, and could see no change in the act of micturition. She was allowed to return home, but was advised to have a re-examination in 6 months.

The patient returned in January, 1955, at our request. Urinary symptoms were absent and residual urine measured less than 20 cc. Mild pyuria (grade 2) was still present. A retrograde cystogram (Fig. 67) showed persistent trabeculation and reflux outlining the lower part of the right ureter and one of the left ureters, which was probably the ureter serving the dilated lower pelvis. Retrograde pyelograms (Fig. 68) showed persistence and questionable increase in the degree of dilatation of both pelves on the right. The lower pelvis on the left appeared to be about the same. The upper pelvis on the left (shown in another film not reproduced here) showed mild pyelectasis.

An evaluation of the situation suggests that, in spite of normal voiding with little or no abdominal straining, an absence of residual urine and only minimal pyuria, dila-

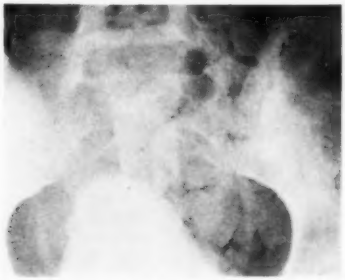

Fig. 67. Retrograde cystogram made in January, 1955. Reflux is present up the ureter on the right and one ureter on the left (most likely the ureter to the lower pelvis).

tation of the upper portion of the urinary tract is slowly but steadily increasing. The most likely explanation appears to be back pressure from ureteral reflux during voiding, and the part played by the bilateral congenital vesical diverticula cannot be overlooked. With 2 ureters opening into the edge and one in the depth of the diverticula, this factor alone might abet and increase both ureteral obstruction and reflux. We have considered the operative procedures suggested by Hutch to obliterate the diverticula and reconstruct the muscular support of the intravesical ureter. We also have considered permanent suprapubic drainage or a return to intermittent catheterization every 6 hours. However, the patient is not interested in further operation at this time. She is now in high school and is living a normal life, with no symptoms. It will be difficult to persuade her to submit to further operative treatment or to live the life of a partial invalid. She is to finish the school year and has agreed to return in 6 months to see what progression, if any, has occurred in the ureteropyelectasis.

When the patient does not remain dry for a substantial period after catheterization or when little or no residual urine is found in association with more or less continuous leakage, the outlook for good results from transurethral resection of the vesical neck is poor. It usually is possible by means of transurethral resection in these patients to eliminate the residual urine, thereby protecting the integrity of the kidneys and ureters, but leakage of some degree continues. This we believe is due to an incompetent external urethral sphincter, a condition peculiar to myelodysplasia; up to now no satisfactory procedure to overcome

this defect has been devised. In an occasional patient, plastic "reefing" operations on the female urethra, such as the Kelly and Kennedy operations, have been successful,[14] but this is the exception rather than the rule. The various "sling" operations likewise have been disappointing.

"Open" operations on the vesical neck should be mentioned. Such procedures usually are done either suprapubically or retropubically. Much discussion has gone on concerning their relative merits compared to those of the transurethral operation. Open operation no doubt is preferable in infants less than two years of age and if the surgeon is not experienced with transurethral resection utilizing small resectoscopes. Generally speaking, the suprapubic approach, with removal of a wedge of tissue from the posterior vesical lip, has not been too satisfactory because it does not open up the distal portion of the prostatic urethra, which often is an important part of the obstruction. The retropubic approach, as described by Burns and Harvard,[2] Burns,[1] Lich and Maurer[25] and Wilson and associates,[31] appears to overcome this defect.

Fig. 68. Bilateral retrograde pyelogram made in January, 1955. There is possible increase of pyelectasis of both pelves on the right. The lower pelvis on the left is about the same; the upper pelvis on the left (not shown in this film) displayed pyelectasis, grade 1+.

The most promising advance, however, so far as open operations is concerned, is the procedure described by Young[32] and Young and Goebel.[33] Using the retropubic approach, they are able to "widen" the vesical neck and entire prostatic urethra in the anterior quadrant, using a longitudinal or inverted Y incision through the vesical neck and roof of the prostatic urethra and closing it transversely or as an inverted V. While the vesical neck is open, if any other obstruction or contraction can be identified, a wedge of tissue is also removed from the posterior vesical lip. In a limited series of cases, including both myelodysplasia and congenital obstruction of the vesical neck, their results have been encouraging and will bear watching.

Results of Transurethral Resection in Myelodysplasia. Elsewhere[15] we have analyzed in detail our results with transurethral resection in

patients who have neurogenic vesical dysfunction caused by myelodysplasia. Although the results leave much to be desired, enough patients have been helped to make the surgical effort worth while. Our experience shows that only one in five patients can be "cured," while a similar number can be improved (elimination of residual urine and improvement in control, but still some incontinence). In general, the results can be classified as good or improved in about 40 per cent of patients. These results are considerably inferior to those in our group of "simple" congenital obstruction of the vesical neck in which approximately two of three patients secure results classified as good or improved. We know of no substantial series of cases of myelodysplasia yet reported by which it may be possible to evaluate the results of open surgical procedures on the vesical neck.

Treatment in "Hopeless" Cases and "Therapeutic Failures." What can be done for patients who have severe lesions in whom all efforts to control urinary and fecal incontinence have failed? What can be done to make their lives more bearable and to eliminate the stench of ammoniacal urine and feces that ostracizes them from society? By far the best efforts to solve this problem have been those of Gross and coworkers,[20] who have experimented with "wet" colostomies and a combination of a regular colostomy plus a bladder made from an isolated segment of sigmoid. In their most recent communication they expressed the opinion that neither of these procedures has produced the desired results. They now consider that a colostomy is not necessary to keep the patient free from fecal soiling. Taking advantage of the fact that the intestine is "sluggish" in these patients, they found that the use of constipating diets and daily cleansing enemas will keep this phase of the problem under control. They warned against allowing fecal impaction to occur, since this results in evacuation of fluid material around the impacted feces, and soiling.

For the control of vesical incontinence they favored permanent suprapubic cystostomy, plus complete severance of the urethra and surgical occlusion of the vesical outlet. They stated that it is remarkable how well some children get along after this procedure. Many are able to keep the suprapubic tube clamped, releasing it only at intervals to evacuate the bladder. Some are able to tuck the clamped tube inside their bathing suits and go swimming; they also may indulge in other sports. The authors warned, however, that this type of "destructive" surgical intervention should be used only after all other forms of treatment have failed. Among the factors they listed as necessary to consider before such surgical treatment is advised are the following: (1) obtain everything possible out of neurosurgical procedures first; (2) educate the patient in methods of emptying the bladder with abdominal and manual (Credé) expression, as well as in exercises to strengthen

the "sphincters"; (3) try surgical procedures on the vesical neck when indicated; and (4) postpone operation until the child is at least three or four years of age to allow for any spontaneous improvement that might occur.

The problem of neuromuscular disease of the urinary tract remains a challenge to the medical profession. Although some progress has been made in its treatment, much remains to be done.

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ENURESIS

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By enuresis is meant the repeated, involuntary passage of urine after the third year of life. Actually, most children are bladder trained during the night, except for an occasional lapse, at 24 to 27 months. Enuresis is common, occurring in 15 to 20 per cent of children.

SYMPTOMS

In the large majority of wetters the child has never been trained for nocturnal control. The history may be confusing, since parents not infrequently state that the child was dry until five or six years of age and only then began to wet. In most of these cases questioning will reveal that the children had been previously picked up during the night and placed on the toilet; when they are no longer picked up, they wet. In other instances the child may himself have awakened and gone to the bathroom; when he stops waking during the night, he wets. In about 8 per cent of cases wetting begins after an infection or a head injury.[10]

The bed is generally wet every night, often several times a night. A dry bed for more than a few nights is unusual, unless the youngster has periods when he wakes up and goes to the toilet.

Day wetting takes place in about 40 per cent of enuretics. The child is aware of the bladder distention. He experiences extreme discomfort to the point at which the urge to empty the bladder becomes irresistible, and the urine pours forth. Occasionally wetting takes place during the day, but not at night. In such instances the youngster, having an irresistible urge to wet, is ashamed to ask the teacher to let him go to the toilet, or the teacher refuses to let him leave the room. At night he gets up and goes to the bathroom, and consequently his bed is dry.

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The central symptom of enuresis is urgency. This varies in intensity, but is always present in true enuresis. Indeed, urgency may be present without bedwetting, the child getting up once or several times a night to empty the bladder.

Boys with "ulcerated meatus," which occurs most commonly in the second and third years of life, are usually potential enuretics. Frequency is often present, and a family history of enuresis can generally be obtained.

The child's emotional response to his infirmity depends on his own personality make-up, on his awareness of the undesirability of his difficulty, and on the attitudes of his parents, teachers and playmates. It should be made clear that, even though the parents may be understanding and accepting, an intelligent child will soon come to appreciate that his symptom sets him apart from the other children and he will suffer accordingly. Some children respond with excessive shyness, others with nonchalance, still others with bravado. Most children do not seem to be deeply affected by their symptom.

Spontaneous disappearance of enuresis ordinarily takes place during early adolescence, but, in the large majority of cases, urinary symptoms persist throughout life. Urgency is most frequent. It may be mild, being simply an exaggerated reaction to emotional tension and cold, conditions which lead to urgency in normal persons; or it may be severe, requiring prompt relief. Persistent nocturia is not uncommon; occasionally the enuresis persists throughout life.

ETIOLOGY

Heredity

In the large majority of cases there is a family history of enuresis in one or both parents and in the siblings.

Socio-economic status is an important contributing factor. Although enuresis is seen in all socio-economic groups, it is more frequent among the poor, where less attention may be given to cleanliness, where inconveniently located toilets (in the hall, for example) make going there at night a difficult and perhaps a frightening experience; where a child sleeps in the same bed with a sibling who also wets. In armies enuresis is fairly common among the soldiers, but rare among officers.

Enuresis occurs among primitive people as well as in civilized societies.

Mental retardation is not a prominent factor except when the retardation is severe as in imbeciles and idiots. In general, children with low intelligence quotients (morons) respond to bladder training as well as those with high intelligence quotients.

PATHOGENESIS

Numerous theories have been proposed to explain the pathogenesis of enuresis. At present enuresis is regarded by most psychiatrists as a manifestation of a general disturbance of behavior. This is not our view.

The following facts strongly suggest that enuresis is based on an inborn structural defect.[2] In the large majority of instances the condition is hereditary. It generally begins early in life, urinary control never having been established. In most cases a remnant (in the form of urgency) persists throughout life. Most of the afflicted children do not appear to be emotionally disturbed.

Further evidence for the organic basis of enuresis is found in observations on urinary secretion in this condition. In 1927 Friedell[6] described a group of enuretics in whom the specific gravity of the urine is lower during the night than during the day, the reverse of the situation in normal children. More recently Poulton and Hinden[10] reported that most children with enuresis pass a much larger amount of urine at night (between 8 P.M. and 8 A.M.) than do normals, far more, in fact, than the child ever passed in one act. In only 12 out of 200 cases did Poulton and Hinden attribute the enuresis to psychogenic factors.

Cystometric studies[7] show that the abnormality in urinary functioning in many enuretics is in the response of the bladder to distention. When the bladder of the normal person is filled to capacity, he experiences a sense of discomfort and a desire to urinate; in the enuretic the desire to urinate is well-nigh irresistible. No striking reduction in bladder capacity was found.

Since the pioneer studies of Campbell,[3] a large number of urologic reports on the appearance of the bladder in enuretics have appeared. Anatomic changes have been described in a sizable proportion of persistent wetters. The most frequent findings were inflammatory lesions of the urethra, trigone, prostate and verumontanum; congenital obstructions along the urethra; foreshortening of the trigone; hypertrophy of the verumontanum; elevation of the inferior margin of the internal urethral orifice and an excavation or depression between the internal urethral orifice and the proximal end of the verumontanum.

Recently, Fisher and Forsythe[5] reported gross abnormalities of the urinary tract in half of the boys with persistent enuresis and in about 40 per cent of the girls. The most frequent findings in boys were valves of the posterior urethra and neurogenic disorder of the bladder; in girls, wide bladder neck anomaly and neurogenic bladder.

Abnormal electroencephalographic tracings have been obtained in a larger proportion of children with enuresis than in groups of children with "neurotic" traits. These findings, first reported by Michaels and Secunda,[8] have been confirmed by other workers.

On the basis of the evidence presented we regard enuresis as a manifestation of a developmental abnormality in the large majority of cases, with psychic factors playing a secondary, but often important, role. This is also the view of Denny-Brown,[4] who states that persistent enuresis is a manifestation of an "inborn, fixed difficulty in inhibiting the bladder (contraction) after the bladder is distended beyond a certain volume of contents."

In a small group of children urinary control is delayed until four or five years. Once urinary control is achieved, there are no further difficulties. In these children one may speak of a developmental retardation rather than an abnormality.

DIFFERENTIAL DIAGNOSIS

Persistent enuresis should be distinguished from the wetting often seen in children following the birth of a sibling. In such instances the wetting is part of general regressive behavior—the child wants to suck from the breast or bottle, to be fed baby foods, to be diapered, and so on. The wetting is voluntary and inconstant, occurs generally when the youngster is sitting on his mother's lap, and is transient, usually lasting only a few weeks.

Urinary incontinence may be a symptom of gross disease of the genitourinary tract, e.g., cystitis, vesical calculus. Here the diagnosis is suggested by the sudden onset of frequency and urgency and painful micturition, and by the presence of red or white (or both) cells in the urine.

The possibility of diabetes mellitus, diabetes insipidus and epilepsy should be considered. Though spina bifida involving the innervation of the bladder is associated with urinary incontinence, spina bifida occulta is not related to enuresis.

Enuresis may be the earliest manifestation of a congenital obstructive lesion of the urogenital tract. Such a condition should be suspected when the urinary stream is small, when starting the stream is difficult, and when there is dribbling. A diagnostic aid is the finding of white blood cells in the urine. The early recognition of such lesions is of the first importance, since major difficulties later on may be prevented by prompt treatment.

TREATMENT

A careful history is necessary to rule out gross organic conditions and to permit evaluation of psychologic factors. Although changes are rarely found, the urine should always be examined at the beginning of treatment.

The treatment of enuresis may be divided into three parts: (1) psychologic management, (2) drugs, and (3) training.

Psychologic Management

Discussions with the parents are designed to inform them about the nature of enuresis and about the futility and possible ill effects of undesirable attitudes. The parents should know that enuresis is an inborn deviation, inherited from one or both of them. The wetting is involuntary and no fault of the child's. Punitive attitudes, such as shamings, scoldings, threats, deprivations, spankings, are useless and may be harmful. Such approaches make the youngster feel unhappy, ashamed, fearful, inadequate, anxious. They may intensify the wetting by unduly agitating the child, by rousing his negativism and, at times, by making him resistant and balky. It is surprising how little understanding is shown by many parents who have themselves been enuretic in childhood.

Explanations to the parents are best given in the presence of the child. His active participation in any line of treatment is essential. It is therefore helpful that he have some understanding of the nature of his ailment. Since suggestion is a potent weapon in the management of enuresis, the child should be repeatedly assured that he can be helped.

During treatment, discussion at home about the wetting should be limited to occasional encouragement and reassurance as improvement progresses.

Drug Therapy

Of the many drugs which have been used in the treatment of enuresis the only one which has endured is belladonna. It is highly effective when used according to a definite plan and for a long enough time. Belladonna has a definite effect on the bladder function of some enuretics. Amberg and Grob[1] found that the administration of belladonna reduced bladder pressure even when the bladder contains larger amounts of fluid than before the drug was given, and that the amplitude and frequency of contractions were reduced. Bladder capacity was increased, and discomfort, when experienced, was slight.

Most failures with belladonna treatment are due to inadequate dosage. A half-hearted approach is bound to fail. Belladonna is generally well tolerated, but since children occasionally show idiosyncrasy, the drug must be increased gradually. A safe initial dose for a child over five years is 10 drops of the tincture. For children who have urgency, with or without wetting during the day, the drug is given three times a

day. When daytime symptoms are not troublesome, it is given only at bedtime. The dosage is increased each day by one drop per dose until a therapeutic or toxic effect is obtained. Thus 10 drops three times a day are given on the first day, 11 drops three times a day on the second day, and so on. The child is seen at ten to 14 day intervals to check on the efficacy of treatment and the appearance of toxic manifestations. It is usually possible to give large doses, up to 30 or 40 drops three times a day (one drop is equivalent to 1/3000 grain or 0.02 mg. of atropine) without inducing toxicity.

The earliest effect is obtained with doses between 10 and 15 drops. Urgency and frequency are greatly diminished, and day wetting usually ceases. Another early effect is a lessening of the amount of urine passed at night.

Belladonna should be continued for eight to ten weeks after the enuresis has ceased in order that training methods may have time to become effective. One rest day a week without medication reduces the tendency to toleration of belladonna. Withdrawal of the drug should be gradual, over a period of two weeks.

Toxic manifestations with atropine are usually mild. The symptom most commonly seen in children is flushing. Dryness of the throat and pupillary dilatation are ordinarily not troublesome. Flushing occurs within a few minutes after ingestion. In such instances the drug should be reduced by two drops per dose.

Belladonna, by relieving the urgency and frequency—and the day wetting when present—makes the youngster more confident of his ability to control the urinary function. In this way the agitation and fear which intelligent children feel are relieved, and thereby a favorable atmosphere for training procedures is produced.

Recently, favorable results have been reported with the use of Thorazine. From 30 to 50 mg. a day are given in divided doses.

Training

Treatment with belladonna should be combined with training. In the management of the enuretic child it is often not only necessary to allay bladder irritability, but to break a long-established habit as well. Limitation of fluids during the late afternoon and a dry supper are sometimes helpful. Having the child prolong the intervals between urinations during the day may be beneficial. After the belladonna has reduced the amount of wetting at night, night awakenings should be introduced. The child is awakened once or twice a night at a fixed time, dressed in bathrob and slippers, and walked to the toilet. He should be completely awake while voiding, since putting a sleeping child on

the toilet has no value in bladder training. The frequency of wakings is reduced as improvement progresses.

A training technique which has met with considerable success is the conditioning apparatus introduced by the Mowrers.[9] The child sleeps on a specially prepared pad. As soon as he starts to wet, a bell rings, and he must get out of bed to turn it off. The device is used with the child's full knowledge and consent. Recently striking success has been reported with this type of apparatus.[11]

Rewards. The system of giving rewards is sometimes effective, especially in young children. The youngster is given a chart on which are written the days of the week, and he is instructed to note the dry and wet nights. A gold star is given for each dry night and a special gift for seven consecutive dry nights. This method is most useful with children five to seven years of age who may be receiving stars for good behavior at school.

The child with enuresis should sleep in a warm bed. Elevation of the foot of the bed helps sometimes. Good results have been reported following urethral dilatation.

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GENITAL TRACT DISEASES IN INFANTS AND CHILDREN

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URETHRITIS

Urethritis, an inflammation of the urethra, is less common in boys than in girls. The process is characterized by discharge which varies from a thin, watery consistency to a profuse purulent type, depending on the variety of the organism and the condition of the urethra.

NONSPECIFIC URETHRITIS

In the *male* the nonspecific type of urethritis is the most common. It is usually secondary to irritation resulting from phimosis, but can be caused by uncleanliness in the circumcised child as well as by foreign bodies. An encrusted or pinpoint meatus often produces a urethritis.

The *symptoms* are frequency and discomfort in voiding. As the process becomes established, the meatus becomes irritated and blood may be observed on the diapers or underclothing. At times the child will void only when the bladder is distended, owing to the discomfort experienced.

The *diagnosis* is usually made from the inspection of the meatus. The discharge should be examined by stained smears to establish the type of offending organism.

Treatment usually starts with sulfonamides or specific antibiotics, although proper attention to cleanliness, together with ample fluids, will go far to clear up the usual case.

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In the *female*, urethritis may occur at any age and is frequently complicated by a vulvovaginitis. Largely the result of poor local hygiene, it may follow infectious diseases and result from the local irritation of pinworms and the introduction of foreign bodies. Though trichamonads are not common in children, they must be suspected.

The *symptoms* are urethral and vaginal discharge with, frequently, excoriation of the labia. The child has discomfort when voiding and usually complains of pain in the area of the genitalia. When the genitalia are greatly inflamed, the little girl will void only when necessary because of the discomfort. In milder cases, frequency is the rule.

The *diagnosis* is usually suspected from inspection of the genitalia. Smears should be made in order to use intelligently the antiseptics available. If foreign bodies are suspected, rectal examination, speculum examination and x-ray may be helpful. It is essential that foreign bodies be removed.

Treatment is usually directed to clearing up the irritative process and counteracting the bacteria which may be present. Strict attention to cleanliness and the use of ample fluids is essential.

When excoriation of the labia persists, the use of Diaprex will rapidly clear up the irritation.

SPECIFIC URETHRITIS

Specific urethritis caused by the gonococcus is now relatively rare. The symptoms are the same as in simple urethritis except that the discharge is more purulent, and discomfort on voiding is usually increased. Penicillin is still the drug of choice, but sulfonamides and other of the antibiotics will usually clear the infection. Erythromycin stands second to penicillin in its effectiveness against the gonococcus.

In any type of urethritis, care must be taken to observe the meatus upon completion of treatment. Strictures or pinpoint openings are common sequelae of this process.

Specific urethritis in the female, formerly prevalent in institutions, is now rarely seen. Contact may be from infected bed clothing, toilet seats and from sexual exposure.

The *diagnosis* is made by the finding of the gram-negative intracellular diplococcus in the urethral or vulvovaginal discharge.

The *symptoms* follow the pattern of urethral infections and result in frequency and discomfort on urination together with acute inflammation of the genitalia.

Treatment is usually effective with the use of penicillin, erythromycin or the sulfonamides. The child should be isolated from other children until the organisms have disappeared.

In any form of urethritis the treatment should be continued until the

tissues are completely free of infection. The chronic urethrotrigonitis of older children and women frequently stems from a simple urethritis in infancy.

PROSTATITIS

Prostatitis in childhood has received scant attention from pediatricians and even less from urologists. Though uncommon in the first decade of life, it may occur, and suspicion of its presence is probably the best means of diagnosis.

The prostate is an accessory sex gland. Endocrine stimulation undoubtedly plays an important role in its function. In the first decade of life the prostate is not so fully developed and the ducts are smaller than in the adult.

Prostatitis is usually the result of inflammation within the posterior urethra and may result from bacterial invasion from the urethra or the bladder. Systemic infections at times involve the prostate. Urethral instrumentation frequently gives rise to prostatitis.

ACUTE PROSTATITIS

Acute prostatitis is a fulminating process in which the glandular structures within the prostate are infected and the ducts become occluded with thick pus and do not drain into the urethra. Pain in the perineum and constitutional symptoms of sepsis predominate. The prostate swells and often becomes fluctuant. Coincident with the increase in size, the urinary stream is often retarded and at times acute urinary retention occurs. Urethral discharge may be present.

Diagnosis

The diagnosis of acute prostatitis may usually be made from the history and a rectal examination. The use of the two- or three-glass test on the voided urine is helpful. Posterior urethral irritation may be reflected by blood in the last voided glass. Infection is present in the expressed prostatic secretion. If this is not obtained on gentle examination of the prostate, the urine voided after palpation will usually contain a greater number of pus cells than that found in the second voided glass.

Treatment

Treatment is directed towards eliminating the infection and promoting adequate prostatic drainage. Though the antibiotics give poor results in chronic prostatitis, they are very helpful in the acute phase of

this disease. Heat, most conveniently given by sitz baths, will materially help the pain and will often reduce the congestion within the gland. After the acute phase has subsided good drainage is essential. If this cannot be accomplished by gentle prostatic massage, then surgical drainage may become necessary.

CHRONIC PROSTATITIS

Chronic prostatitis may follow an acute prostatic infection, but usually is the result of repeated low grade irritation. In many cases no pathogenic organism may be cultured from the prostatic secretion. Chronic congestion of the prostate and posterior urethra seems the most plausible factor in the etiology of prostatitis. The high incidence of this disease in young boys gives credence to the findings of Campbell[5] that masturbation is a common cause of prostatitis in this age group.

Symptoms

The symptoms of chronic prostatitis in boys are variable. The inflammation in the posterior urethra may be sufficient to cause urinary frequency. Rarely will this result in the "terminal" type of hematuria. The recurrence of enuresis in older boys may point to prostatitis. The referred pains, common in adults, are generally absent. A thin, sticky urethral discharge, usually free of bacteria, may be the only symptom.

Diagnosis

Diagnosis depends largely on the recognition of its possibility and the finding of infection in the expressed prostatic secretion. Shreds in the first voided glass of urine should help in the diagnosis.

Treatment

Treatment of chronic prostatitis depends on elimination of the irritative factors which are the cause of the condition, a statement which is easier to write about than to accomplish. Good drainage of the prostatic acini and ducts is essential. This can best be accomplished by gentle, and not too often repeated, prostatic massage. Elimination of any urinary obstruction and the clearing of such systemic infections as might be suspected of contributing to the prostatitis are essential. The use of chemotherapy in chronic prostatitis has not met with much success, but the occasional good response to drugs is an indication for their use.

TORSION OF THE SPERMATIC CORD

Torsion of the spermatic cord, which often goes under the misnomer of torsion of the testicle, is not common, but, because of the critical time element which attends its management, it should be suspected and, if possible, differentiated in all acute and painful swellings of the testicle.

Etiology

The testicle arises from the genital ridge and early in embryonic life fuses with the mesonephric tubules which form the epididymis. The gubernaculum acts as a guide and gives some help in the descent of the testicle into the scrotum. On its way downward a partial covering of the peritoneal fold becomes the tunica vaginalis. It is not surprising that abnormalities of this complex structure may arise. Imperfect descent, failure to close approximation of the epididymis with the testicle, abnormal topography of the tunica vaginalis, absence or extreme length of the gubernaculum, abnormal attachment of the cord and combinations of these anomalies can give the impetus out of which torsion of the spermatic cord develops.

Torsion of the cord results from an axial rotation. This may be supravaginal in which the testicle, epididymis and the tunica vaginalis twist within the scrotum. This is rare. The most frequent form is vaginal, in which the testicle and epididymis rotate within the cavity of the tunica vaginalis. In either event the twisting of the cord results in vascular obstruction.

Torsion of the spermatic cord has been reported in the newborn with pathologic evidence that the rotation took place in utero. The highest incidence comes during adolescence.

Symptoms

The condition is characterized by the sudden onset of pain in the affected testicle, often of sufficient severity to produce nausea and vomiting. Varying degrees of shock may be present. The leukocyte count is not usually elevated at the onset of symptoms, and the temperature is often normal. Edema and swelling rapidly develop.

Diagnosis

The most important factor in diagnosis is suspicion of the presence of torsion. The high position of the testicle, the inability to delineate the epididymis and the testicle, together with the history of sudden onset, should be suggestive. A definitive diagnosis can be made only on surgical exploration.

Torsion of the cord must be differentiated from several conditions; epididymitis is the most common. Here the onset is slower, there is some history or findings of infection, and the temperature and leukocyte count are higher. According to Prehn,[14] elevation of the testis in acute epididymitis relieves the distress, while in torsion the pain is increased. In orchitis the history of mumps, or other systemic disease, the slower onset and milder symptoms, together with the usual ability to palpate the spermatic cord, give the needed clues to diagnosis. Strangulated hernia, especially when the testicle is undescended, often presents a difficult differential diagnosis. The signs of intestinal obstruction with increase in vomiting and tympanites will generally help to evaluate the problem.

Treatment

Treatment for torsion of the spermatic cord is surgical. The damage to the testicle depends upon the degree and duration of the condition. If viability can be demonstrated, then the organ can be sutured to the scrotum. If more than a few hours have elapsed since onset, the testicle becomes gangrenous and orchiectomy is necessary. The question of anchoring the contralateral testicle is still moot. We believe that this should be done.

HYDROCELE

The testicle, in its descent from the abdomen to the scrotum, is preceded by an evagination of peritoneum which eventually enfolds the testicle and epididymis and forms the tunica vaginalis, into which the testicle projects. This, the smallest of the cavities derived from the celom, normally contains a few drops of clear serous fluid. Any appreciable increase in the amount of fluid is called a hydrocele.

Hydrocele as an entity has been recognized for centuries. Celsus gives a good description and indicates that the Greeks understood the pathology involved as well as had a name for the condition. Percival Pott, when chief surgeon of St. Bartholomew's Hospital, wrote a comprehensive monograph on the subject.

Etiology

The extensive literature which has developed on hydrocele has dealt mainly with treatment and statistical analyses. Though pathologic conditions within the cord or scrotum can produce a hydrocele, more than half of the cases are seen in patients in good health, without demonstrable disease of the scrotum or its contents. Experimental work on

hydrocele has been retarded because the common laboratory animals have a patent processus vaginalis. Only man and possibly anthropoid apes possess a tunica vaginalis which does not communicate with the peritoneal cavity.

Two Italian workers, Monarci and Torraca,[16] injected chemicals into the hydrocele sacs in men and noted the absorption time. In 1930

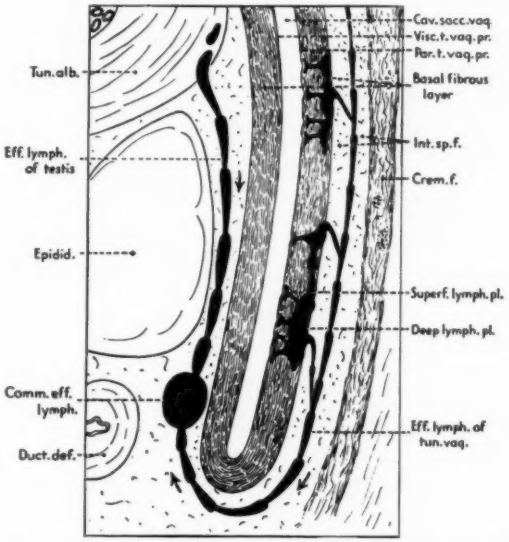

Fig. 69. Section of testis and tunica vaginalis showing deep and superficial lymphatic plexuses which occur in the basal fibrous layer of the parietal tunica vaginalis. The efferent lymphatics of the tunica vagnialis course around the parietal tunica vaginalis from the medial to the lateral side and enter a common efferent lymphatic which also receives efferent lymphatics of the testis. (After Allen. Reprinted from the Anatomical Record with permission of the Wistar Institute.)

Huggins and Entz[11] reported their experiments on quantitative absorption of phenolsulfonphthalein from normal men with and without hydrocele. They found that absorption from the tunica vaginalis testis was much slower than from any of the other serous cavities and that the absorption of dyes in hydrocele is much less.

The anatomic studies of Rinker[15] indicate that the tunica vaginalis testis has a well defined lymphatic system. In conjunction with those of Allen,[1] these experiments were extended to a clinical sphere which showed that in hydrocele the lymphatics are permanently damaged. These studies further indicate that the lymphatics are not adequately developed at the time of birth and that in the congenital type of

hydrocele this may explain the absorption of the fluid during the early months of life. All these studies indicate that the formation of hydrocele is due to an imbalance between secretion and absorption.

The classification of hydrocele depends on the location, type, and degree of closure of the processus funicularis. The *acute hydrocele* indi-

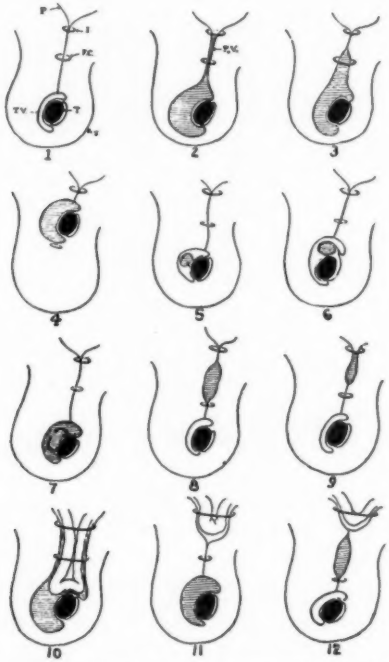

Fig. 70. Schematic representation of various types of hydrocele. 1, Normal relationship. 2, Congenital hydrocele. 3, Infantile. 4, Hydrocele of undescended testicle. 5, Hydrocele of testicle. 6, Hydrocele of epididymis. 7, Bilocular. 8, Hydrocele of cord. 9, Hydrocele of hernial sac. 10, With hernia (congenital type). 11, Hydrocele of tunica vaginalis with hernia. 12, Hydrocele of cord with hernia. (Campbell: Pediatric Urology.)

cates, as the name connotes, that the fluid develops in response to some pathologic process within the testicle or its structures. This may be the result of trauma, inflammatory processes or the reaction to some systemic disease. All other accumulations of fluids would be of the *chronic* type. When the processus funicularis is open, the condition is called *congenital*. If the tunica and funicular process are closed only at the internal ring, this is classed as *infantile*. A hydrocele of the cord is limited to that structure just as the enlargement of the cavity of the

tunica vaginalis goes by that name. Hernia may complicate any type of hydrocele. The familiar schematic representation by Campbell[3] is self-explanatory.

Symptoms

In the *acute* hydrocele, pain depends upon the degree of primary disease within the testicle or epididymis and is in proportion to the rapidity of development of the fluid. In the *chronic* cases the symptoms are minimal and are usually reflected in the discomfort caused by the actual degree of swelling and weight of the tumor.

Hydroceles in *infancy* are more prevalent than in childhood, which bears out the findings of Rinker concerning the delayed development of lymphatics. In adolescence the incidence rises. This may be due to the increased incidence of accidents in the growing boy.

Diagnosis

Diagnosis of hydrocele in infancy and childhood should not be as complicated as in the adult. The pear-shaped tumor mass pointing toward the external inguinal ring should be suggestive. The hydrocele sac is usually thin, making for easier transillumination than in one of long duration. The smooth contour of the mass together with dullness on percussion and absence of bowel sounds and the inability to reduce it (except in the congenital type) usually differentiates the hydrocele from a hernia. Coexistent hernia will make these findings difficult to evaluate.

The hydrocele must be further differentiated from spermatocele in the adolescent boy, and this can usually be done only by aspiration of the typical sperm-loaded fluid. The position of the spermatocele is usually behind the testicle rather than in front as is usual with hydrocele. Hematocele, denoting blood within the tunica vaginalis, can sometimes be suspected by a history of recent injury. It is usually not translucent. Superficial ecchymosis may aid in this differential diagnosis. Chylocele is a tropical disease not usually seen in North America. There are often other signs of filariasis, the etiologic factor in the development of this process. The aspirated fluid may contain filaria. Chronic edema may often simulate hydrocele, but here again the coincident presence of edema and the pitting of the skin of the scrotum on pressure will usually give the necessary clue. Testicular tumors are rare in infancy and childhood, but their presence must be suspected, and the two conditions may coexist. Almost universally they are not translucent, and their weight is greater than that of a hydrocele. A hydrocele in an un-

descended testicle may be very confusing. In a patient with tumor and an imperfectly descended testicle the condition must be suspected.

Treatment

Treatment of hydrocele is well established. This consists of (1) palliative therapy—either watchful waiting or tapping. In infants the swelling can be watched. If it does not absorb within a reasonable time or if the testicle becomes tense, then more active treatment is indicated. We do not favor tapping of hydroceles in infancy or childhood.

2. Introduction of irritative substances into the hydrocele sac is older than radical surgery. The ideal to be obtained is an obliteration of the space by the presence of adhesions. Many excellent series have been reported, but it is our opinion that this method should not be used in children.

3. Radical surgery in our opinion is the procedure of choice in childhood. A steady improvement in technique has made this operation almost universally successful.

It is our practice to dissect the sac down to the serosa as described by Young.[18] We excise the edges of the sac away from the testicle and epididymis, but do not evert the edges around the cord. We have not found it necessary to employ the method of Wolf,[17] who uses interrupted, interlocking figure-of-eight sutures, but this would be advantageous in a case in which unusual bleeding occurred. A small dependent Penrose drain is always used for the first 24 to 48 hours.

The most troublesome sequelae of the radical operation for hydrocele are hemorrhage, induration, infection and involvement of the testicle. Careful attention to bleeding at the time of operation, proper use of antibiotics and care in handling of the testicle will usually obviate most postoperative complications. Edema and induration of the scrotum is usual, but rapidly subsides with careful elevation and "gentle" surgery. We warn the patients and their parents of this occurrence before operation.

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TUMORS OF THE UROGENITAL TRACT IN INFANTS AND CHILDREN

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Tumors of the genitourinary organs of children fortunately are rare. Their importance, however, is out of all proportion to their incidence because of the high mortality. Though malignant diseases, such as these, which often progress far without producing significant symptoms always will be serious, a certain number of lives now lost can be saved by earlier diagnosis and more appropriate initial treatment. With few exceptions, a urologic examination is required to establish an early diagnosis. Family physicians should not delay these investigations through fear of the effects of urologic procedures, because thorough examinations can be performed without injury to the youngest infant of either sex by a properly trained urologist using modern instruments. As soon as a tumor has been found, one should decide to attempt a cure in every suitable case even though this may require an extensive operation. Experience has shown that infants recover rapidly after major surgery if they are protected by the usual safeguards now commonly taken with adults.

So that this contribution may have the greatest clinical value, I decided to limit this discussion to primary tumors of the kidney, bladder, prostate and testis which comprise practically all the neoplasms of the genitourinary organs in childhood. A complete classification of all tumors of the genitourinary organs in the young has been made by Campbell.[1]

WILMS' TUMORS

Incidence

Statistical studies made by us of the clinical material at the Memorial Hospital and by others of the incidence of all malignant tumors of

infancy show Wilms' tumors second in frequency only to tumors of the eye. In adults renal tumors comprise only about 0.5 per cent of all cancers, but in children they approximate 20 per cent. With few exceptions, all are embryonal adenomyosarcomas or Wilms' tumors, by far the most common tumor of the genitourinary tract in infants.

Wilms' tumors are congenital, embryonal, mixed tumors. They arise from the kidney anlage. The disease has been found in the seven months' fetus, and upward of 60 cases have been reported in adults, but it is exceedingly rare after the seventh year. The average age of patients when the tumor has been discovered is about three years. The sexes are affected equally.

Etiology

Since these tumors may show marked variations in the degree of differentiation of their component cells and in the number of tissues represented, it seems reasonable to suppose that they may originate at different developmental periods of the embryo. If the tumor arises before the urogenital ridge has formed the nephrotome, multipotency of these cells may account for the elaboration of smooth and striated muscle fibers, fat and cartilage cells and sarcomatous and tubular elements. At a later stage, if the renal blastoma or nephrotome is the predominant contributing structure to the tumor, primitive renal tubules or even primitive glomeruli may be recognized. It is likely that the stage of embryonal development at which Wilms' tumors arise is a matter of great clinical importance, because this factor may modify not only the structure of the growth, but also its natural history and, to a considerable degree, its response to various types of treatment.

Pathology

Grossly, these tumors are usually unilateral, although in Wilms' collected series 7.2 per cent were bilateral, and Kretschmer and Hibbs found bilateral occurrence in 12 per cent. The bilateral origin of Wilms' tumors may be somewhat exaggerated by these figures, which, in a number of instances, were based on autopsy examinations. Usually at the time of death, Wilms' tumors have metastasized widely, and it is impossible to determine whether involvement of the contralateral kidney was primary or metastatic. The tumor may occur in any part of the kidney, although usually the lower half is first involved. At first the growth is always within the renal capsule. When this is ruptured, extension rapidly follows the routes of least resistance. Practically all Wilms' tumors are surrounded by a dense capsule which completely separates them from the renal parenchyma. This capsule usually re-

mains intact until the growth is large. Because of this encapsulation, many observers have described Wilms' tumors as "in" but not "of" the kidney. The capsule also is largely responsible for the infrequency of urinary signs.

Wilms' tumors grow aggressively. They may extend toward the renal pelvis, pushing kidney tissue outward to form a pseudopolyp, or the growth may protrude from the hilum. The kidney may retain its shape, but in many cases it has been found fixed like a small cap on the tumor mass. The tumor usually is bluish and smooth, although irregular lobulations are present in more advanced stages. On section the substance is soft and grayish-white or yellow. In parts it may look medullary, fibrous, gelatinous, vascular or edematous. Situated retroperitoneally, the tumor displaces the colon forward and mesially. On the right side it may press against the duodenum and obstruct it. After the renal capsule has ruptured, the disease is likely to extend through the peritoneum and involve the omentum and adjacent organs of the abdominal cavity. All the viscera may be affected. The walls of large blood vessels, especially veins, and the ureters have been destroyed; even the diaphragm is but a temporary barrier. These tumors may grow to a weight of 5000 gm., which may be 25 per cent or more of the weight of the infant.

The veins of Wilms' tumors are comparatively large, and their walls are thin and fragile. They frequently rupture spontaneously with the production of infarcts. Often they are invaded by tumor cells. As a result, although lymphatic extension occurs, the earliest demonstrable metastases are usually blood-borne and are found in the lungs, the brain or the skin. The majority of the patients seen by us as early as a week after the discovery of their primary tumors had demonstrable metastases, while patients examined after a greater delay had metastases with even greater frequency. On the other hand, there was a small group of children with no metastases several months after the primary tumor had been found. This well illustrates the considerable biologic differences which may be found in different Wilms' tumors.

Histologically, Wilms' tumors are composed entirely of tissues of mesodermal origin. In some specimens the predominant cells are round, hyperchromatic and undifferentiated; in others, differentiation is more complete, and one can see reproductions of renal tubules and glomeruli. Interspersed among these structures of renal blastema origin may be found other tissues such as smooth tissue, striated tissue, myxomatous tissue and, rarely, cartilage and fat.

The epithelial elements of the tumor consist of tubules of variable sizes and shapes lined by cylindrical or cuboidal cells. The basement membrane is often imperceptible. The glandlike tubules are usually single-layered and have a tendency to form cysts. In some areas the

epithelial tissues form solid cords or strands. Abundant mitoses in the cells of these tubules indicate their activity in the histogenesis of the tumor. Smooth muscle fibers are found in these tumors with some regularity. Ribbert and Busse assert that the rarer striated muscle fibers develop from them by metaplasia. Other structures such as fat and myxomatous tissue are only occasional components of the tumors, but they occur sufficiently often to justify the use of the term "mixed tumor."

Symptoms

In common with all other kidney tumors, Wilms' tumors produce no symptoms until comparatively late in their life history. When symptoms can be detected, the disease is far advanced. As the tumor grows in the infant, there is a gradual enlargement of the abdomen which may be accompanied by constipation and malaise. After a time, in the majority of cases entirely by accident, a large mass is discovered in one side of the abdomen. If growth continues, it is not long before there is an augmentation of symptoms such as vomiting, loss of weight, asthenia, anorexia, an increased rate of tumor growth, and the appearance of tortuous, dilated, superficial veins. Before long the terminal stage is reached with ascites, marked emaciation, a tremendously enlarged abdomen, and perhaps obvious metastases. Death is usually caused by cachexia, occasionally by intercurrent disease.

We have seen nearly 100 patients with Wilms' tumors, but this group is too small for a close study of the initial symptoms to have statistical significance. In two thirds of the patients the first suggestion of disease was the sudden, accidental discovery of a large mass in one side of the abdomen in an otherwise healthy infant. About one patient in eight had pain in the abdomen. About one in ten showed asthenia and malaise. A single patient had hematuria, and but one suffered from frequency of urination.

Pain was seldom an important symptom. In an infant it is always difficult to evaluate. It may be colicky, associated with constipation, or it may occur when the rapidly growing tumor exerts tension on the renal capsule or traction or pressure on adjacent organs.

Hematuria, usually painless, has been reported in between 10 and 25 per cent of children with Wilms' tumors, in contrast to an incidence of between 75 and 80 per cent of adults with tumors of the renal parenchyma. This striking difference probably is due to the encapsulation of Wilms' tumors. Not infrequently the bleeding is from the congested parenchyma of the kidney rather than from the tumor proper. Hematuria is always intermittent, with recurrences at irregular and sometimes

widely separated intervals. In common with all bleeding from the kidney, the blood is equally mixed with all the voided urine.

Urinary symptoms are unimportant and usually appear insignificant, probably because the tumor capsule separates the growth from the renal pelvis and parenchyma. For the same reason cytologic tests of the urine appear to have little promise. Erythrocytes sometimes are found on microscopic examination, but many tests may show normal urine, especially when the diseased kidney does not function because of pressure atrophy. Urinalysis may aid in detecting the onset of infection, and it may be significant when albuminuria follows pressure on the tumor.

Fever may be the first and, for a time, the only symptom. It is frequent with Wilms' tumors, as it is in children who have lymphosarcoma or endothelial myeloma. A majority of our patients had intermittent fevers ranging from 101.5° to 104° F. The temperature elevations seemed unrelated to the stage of the disease.

Diagnosis

A palpable tumor is an important discovery in either a child or an adult, but in a child it may be the only diagnostic sign. There may be difficulty in feeling the tumor if the child is obese. Also, in young infants, the kidney normally lies deeper in the pelvis than in adults. Careful bimanual palpation of a Wilms' tumor may demonstrate its location, size, shape, consistency, mobility, and tenderness on pressure. The surface is usually smooth, although it may become lobulated. In most cases the consistency is elastic, although, when necrosis occurs or bleeding takes place in its substance, the tumor may be as soft as in hydronephrosis. Mobility depends on the size of the growth and the amount of available space remaining in the abdomen, and, for a time at least, primary tumors are not adherent and move with respiration.

Differential Diagnosis

The clinical features of a large tumor apparently connected with the kidney of a young child should make one suspect a Wilms' tumor and, without delay, undertake measures to establish a diagnosis. The following intra-abdominal masses occurring in infants must be differentiated from a Wilms' tumor, but, since a diagnostic error could prove fatal, one should not depend on one's unaided clinical judgment:

1. *Lymphosarcoma of retroperitoneal lymph nodes* is centrally located and is surrounded by resonant intestines. In a Wilms' tumor, resonance is mesial to the abdominal mass. Regional lymph nodes are more frequently affected by lymphosarcoma.

2. *Tumors of mesenteric lymph nodes* such as lymphosarcoma, malignant lymphogranuloma or tabes mesenterica are massive, somewhat superficial and situated near the umbilicus.

3. *Suprarenal tumors* in children are often associated with disturbances of the endocrine system.

4. *Tuberculous kidneys* are seldom as large as Wilms' tumors. Urinary symptoms are more prominent and laboratory findings are often pathognomonic.

5. *Hydronephrosis,* often impossible to differentiate by palpation, should be recognized by a urologic examination or by aspiration.

6. *Polycystic disease* is always bilateral, but one kidney may be considerably larger than the other. Retrograde pyelograms furnish the best diagnostic evidence. The cysts seldom are large in infancy.

7. *Tuberculous peritonitis* is sometimes difficult to differentiate from a Wilms' tumor. The general physical examination, doughy consistency of the abdomen, chest films and family history should furnish clues.

8. *Hepatic tumors* are rare in children. Although they seldom are accompanied by jaundice, there usually are severe gastrointestinal symptoms and abdominal pain.

9. *Ovarian tumors* are rare in childhood. Usually they are bilateral and can be palpated bimanually with one finger in the rectum.

10. *Splenomegaly* is more superficial than a Wilms' tumor of the left side and is usually situated higher in the abdomen. Blood examinations aid in detecting leukemia, malaria or syphilis.

11. *Pancreatic tumors* are rare in children and cause unusually severe gastric symptoms and intractable pain.

12. *Fecal tumors* are more superficial than Wilms' tumors, and are freely movable and accompanied by obstipation or intestinal obstruction. Roentgenograms taken after a barium enema usually clear up this diagnosis.

13. *Psoas abscesses* should be differentiated by their more chronic febrile course, pain in the vertebral column and characteristic roentgenographic changes in the spine.

Urologic Examination

As soon as the examiner has palpated the tumor carefully and has considered its possible nature, a urologic examination should be made to demonstrate accurately the identity of the mass. Though diagnostic procedures must be carried out methodically and nothing important should be omitted, it is essential that no time be wasted, because, if the growth is a Wilms' tumor, successful treatment can be given only before metastasis occurs. When a Wilms' tumor is palpable, metastasis

either has occurred or is imminent. In a well regulated urologic department a diagnosis should be made in a few hours.

Excretion urograms should be made first and usually are sufficient to demonstrate the mass pressing upon the kidney and deforming the configuration of its pelvis and calyces. The contrast medium should be injected into a vein and exposures made promptly, because in infants the kidneys excrete the material so promptly that all of it may be in the bladder within five minutes. Campbell[1] has shown that if the baby is given his bottle a short time before the films are exposed, the stomach becomes distended with air and often provides a dark background upon which kidney changes, especially those in the right side, stand out in clear contrast.

If the tumor compresses the kidney so greatly that no contrast medium is visible, retrograde pyelograms can be made through ureteral catheters introduced by using an infant's cystoscope. This requires general anesthesia, but the importance of diagnostic accuracy far outweighs this disadvantage. A chest film then should be made.

In rare instances the diagnosis of a Wilms' tumor may be doubtful even after careful roentgenologic studies have been made. Uncertainty, however, should not greatly delay treatment, because a palpable mass connected to the kidney must be removed. The worst possible error, prompted by diagnostic uncertainty, is to expose the tumor and excise a portion for frozen section diagnosis. In my experience this procedure always has been followed by local recurrence.

Treatment

If a tumor in the kidney has been found and careful search shows no evidence of metastasis, an adequate cancer operation should be planned promptly and carried out. The infant subjected to surgery, like the adult, should be provided with every possible safeguard, including preoperative measures to improve his general resistance. Experience has shown, however, that the great majority of patients with Wilms' tumors who, when the tumor is discovered, are free from demonstrable metastases are in good general physical condition and require no delay for preoperative supportive treatment.

The loin incision is obsolete for the removal of any kidney tumor, and the approach to a Wilms' tumor should be through either a thoraco-abdominal or a Nagamatsu incision, both of which freely expose the tumor region, permit early ligation of the renal pedicle and make possible removal of the growth within the perirenal fat.

Roentgen Therapy. External roentgen therapy should be given in all cases after removal of the growth. Though postoperative irradiation is recommended only on an empirical basis, improved end results have

followed its use. Irradiation usually can begin within a week of the operation. In children the 250-kilovolt unit is sufficiently powerful. Treatment is given through anterior, posterior and lateral portals directed toward the region of the renal pedicle, but covering the entire area previously occupied by the growth. A tumor dose of 2500 roentgens is desirable, but more frequently 2000 roentgens is better tolerated. The daily dose of radiation must be determined for each individual. One may start with 200 roentgens daily and reduce it if necessary. Usually children are intolerant of radiation as compared with adults. Blood cell counts should be made every five days during radiation therapy; if the white cells fall significantly, transfusions of whole blood should be given.

If metastases have been discovered, the patient is incurable by presently available therapy. He should be considered inoperable, and as much palliation as possible should be given with external radiation. Usually this is little enough, but radiation is the best agent known for diminishing pain and prolonging life.

The writer no longer recommends preoperative irradiation because (1) it delays surgical removal of the tumor; (2) there are great possible differences in the radiosensitivity of different Wilms' tumors; (3) even though the tumor rapidly shrinks under irradiation, viable portions remain which could produce metastases even during treatment; (4) irradiation probably promotes infarctions in the growth. This could facilitate the entry of tumor cells into the circulation. (5) More adequate and safer operations now can be performed, and it is of slight importance to shrink the tumor before its removal. Patients with Wilms' tumors should not be treated with radiation alone for the reasons stated, and also because the curative dose of radiation for any Wilms' tumor is unknown. Furthermore, irradiation may produce subsequent developmental deformities in the patient even though the tumor may be controlled.

Results. No published end results of the treatment of Wilms' tumors comprise a sufficiently large number of patients to have statistical significance. Probably the majority are treated by surgeons with little or no previous experience with the disease, and the results are poor. On the other hand, a survival of approximately 50 per cent has been achieved by Gross at the Children's Hospital in Boston. This is much superior to the experience of others and must be attributed largely to greater diagnostic acumen of physicians in and about Boston who refer to him their patients before metastasis has occurred. Certainly in large medical centers there is general unanimity regarding the proper treatment of this disease and in the knowledge that treatment must be given promptly, but in our experience the great majority of the patients when first seen had metastases and could not be saved, although all known

forms of treatment were available and were used without delay. In general, small infants appear to have a higher survival rate, presumably because they are handled frequently and their tumors are thus discovered earlier. What is certain, however, is that early diagnosis and prompt surgical removal before metastasis occurs is the only successful treatment now known for Wilms' tumors.

TUMORS OF THE BLADDER

In a study of the organs involved by primary tumors in infants, Picot places the urinary bladder seventh in frequency. Bladder tumors in infancy, however, are rare. Deming,[4] in 1924, found but 64 occurring before the age of ten years in the medical literature. Practically all were sarcomas. Khoury and Speer, in 1944, reported eight cases of rhabdomyosarcoma from the literature, and in 1952 Mostofi and Morse[6] described ten specimens of this disease from the Bladder Tumor Registry of the American Urological Association in the Armed Forces Institute of Pathology. The most common tumor of the bladder in infants and the one studied most carefully by modern urologic methods appears to be the rhabdomyosarcoma, or sarcoma botryoides, and it will be the subject of this discussion.

Though the disease has appeared in children as old as nine years, the majority are less than two years of age at the time of the first symptom, and they may be newly born. Boys are affected twice as frequently as girls. The embryonic origin of these tumors is not clear, but Mostofi and Morse consider that they "arise from embryonal tissue capable of differentiation into myxomatous tissue, fibrous tissue, and striated muscle. Histologically the tumor may consist predominantly of one or any combination of these cell types. In its most differentiated form the growth shows unmistakable striated muscle." If this is true, the majority of the older reports collected by Deming were, in fact, descriptions of the same disease. The numerous apparent differences in the pathologic diagnoses were the result of classifying the tumors on the basis of the type of tissue which predominated.

Pathologic Anatomy

The great majority of these tumors grow from the trigone and region of the internal urethral orifice, although, in rare instances, they have been found arising from other locations in the bladder. The growth consists of a cluster of numerous rounded and elongated grapelike projections, well described by the term "sarcoma botryoides." Ulceration usually does not occur until the growth is considerably larger than if

the tumor had sprung from the bladder epithelium, and as a result hematuria is seldom the initial symptom. While the base of the tumor spreads toward the ureteral orifices, ultimately to cause stenosis, the grapelike projections produce much more striking disability by obstructing the internal urethral orifice as the infant attempts to void. Polypoid projections may be forced into the urethra by the effort to urinate and, especially in little girls, sometimes may be seen protruding from the external urethral meatus.

All forms of treatment short of cystectomy have proved futile, and recurrences which appear to grow much more rapidly than the primary tumor usually can be recognized within a few days or weeks of the application of locally destructive agents. At this time or soon after, the ureteral orifices become obstructed. Unless this is relieved, death follows from pyelonephritis and kidney failure. The inadequate treatments which are followed promptly by aggressive local recurrences may also encourage spread of the tumor beyond the bladder, although, generally speaking, the disease does not metastasize until intravesical involvement is extensive.

Symptoms

The predominant symptoms are produced by a mechanical obstruction of the internal urethral orifice. It increases as the tumors grow and becomes aggravated when infection follows urinary retention. At first the infants strain and grunt in their attempts to void, and there may be blood in the urine. Between efforts to void, the babies appear to be comfortable. Before long, urination is more frequent and more difficult, and the infant is likely to become sleepless. When infection occurs, the tumor ulcerates and bleeding becomes more frequent and more profuse, and the patient suffers more from tenesmus.

Physical Examination

The appearance of an infant straining to void small quantities of blood-tinged urine is clear evidence of obstruction, although whether it is due to a stone or a tumor is uncertain. Often a greatly distended bladder can be palpated if not seen. Bimanual rectal and abdominal palpation may detect induration of the bladder base, but usually no abnormality can be detected until later in the course of the disease or after a postoperative recurrence has developed. Immediate temporary relief of the infant by catheterization usually is possible, and the suprapubic tumor disappears as a considerable amount of urine is withdrawn. Before the infant cystoscope was devised, clinicians sounded the bladder in search of a stone, but this no longer is recommended.

Urologic Examination

A urologic examination should be made without further delay. Excretion urograms usually show whether or not there is dilatation of the upper urinary tract, the presence or absence of a stone in the bladder or a relative filling defect in the bladder due to a tumor.

Cystoscopic examination under general anesthesia shows a tumor which usually springs from the trigone and appears to involve the region of the internal urethral orifice. It consists of numerous edematous polypoid structures, some of which are rounded and raised but a short distance above their base, while others may be elongated. The latter project into the bladder lumen and tend to fall against the cystoscope lens, obstructing vision. If the tumor is located in another part of the bladder, its features usually can be observed more clearly, since the usually dilated viscus is easily distended, at least to the extent of separating the observation lens from moving portions of the growth. Occasionally the bladder appears to be filled with tumor, and clear vision is exceedingly difficult.

Although the tumor base usually is red from congestion, at the first cystoscopic examination there is likely to be no visible ulceration. The polypoid projections are edematous to a varying degree and usually are grayish-pink. Since polypoid overgrowths in adults usually are manifestations of inflammation, and since the examiner almost always is viewing this lesion for the first time, the growth potential of the tumor usually is underestimated.

It is difficult to remove satisfactory tumor specimens through the infant cystoscope, and the infant resectoscope rarely is used because prompt transvesical treatment to relieve obstruction is necessary. Therefore, most first specimens have been removed when the tumor has been exposed for the purpose of applying the first treatment.

Using modern histologic techniques and modern terminology, Mostofi and Morse[6] describe the microscopic appearance of the tumor as follows:

> The transitional surface epithelium may be intact . . . or ulceration and necrosis of tissue may occur. The lamina propria is replaced by myxomatous tissue containing stellate cells, and a few polymorphonuclear leukocytes, lymphocytes and monocytes. . . . Thus in superficial biopsies early in the disease the true nature of the lesion may be entirely masked by the sparsity of neoplastic cells and the presence of inflammatory reaction. In other cases squamous metaplasia of the surface epithelium and glandular formations may be found, simulating infiltrating carcinoma. . . .
>
> The tumor may contain foci made up of interlacing bundles of slender, spindle-shaped mesenchymal cells with acidophilic cytoplasm, forming longitudinal fibers and surrounding an elongated hyperchromatic nucleus. . . . These may alternate with myxomatous areas containing a scattering of monocytes, lymphocytes and granulocytes.
>
> Cells of three types have been described by Houette. The first type is a rather large spherical cell with a small amount of faintly acidophilic cytoplasm and a round

or oval vesicular nucleus, quite suggestive of a lymphocyte except that the nuclear material is more clearly visible. These cells are the primitive or blastoma cells of Masson. They may display occasional mitotic figures. The second type consists of multinucleated giant cells in which a small amount of vacuolated or acidophilic cytoplasm surrounds from 5 to 20 small hyperchromatic centrally situated nuclei. The third type includes the more differentiated oval or spindle-shaped cells with eosinophilic cytoplasm, which may show longitudinal fibrils at one or both ends. . . . Other cells may have both longitudinal fibrils and cross striations in their cytoplasm. These striated muscle cells, which are infrequent in the superficial portions and in the tissue removed early in the course of the disease, become more abundant in the deeper portions and in tumor tissue removed later in the disease.

. . . The characteristic microscopic picture in the early stages of the disease is that of a loose myxomatous tissue through which spindle-shaped cells and varying numbers of inflammatory cells are scattered. Some of the spindle cells may show cross striations. This loose edematous tissue gives rise to the grapelike appearance of the tumor, justifying the use of the term sarcoma botryoides to differentiate these tumors from other rhabdomyosarcomas. The three cell types that have been described appear in later stages of the disease when the striated muscle cells can usually be found with ease.

Treatment

All demonstrable features of this disease, at the time of its discovery, tend to mask its highly malignant nature. These considerations, and the fact that the patient is usually a small infant, prompt the surgeon to use an inadequate initial type of treatment. The sequence of events described in the literature consists in suprapubic cystotomy usually with thorough electrocoagulation of the growth. Segmental resection of the bladder also has been performed when the location of the tumor was favorable. In all cases the tumor recurred promptly and grew rapidly. Now the cystoscopic examination clearly shows a serious bladder tumor, and biopsies reveal the characteristics of a highly malignant growth. Further cauterizations at this time with or without local applications of radium have been futile. Soon the ureters become obstructed at their vesical junctions, and death from kidney failure follows.

The only successful treatment known to me for rhabdomyosarcoma in infants is cystectomy. I have performed uretero-intestinal anastomosis and cystectomy in one stage for this disease in three instances, two of the patients being infants. One of the infants died of tumor recurrence a year later, while the other patient, operated upon in 1949, is living without evidence of recurrence or metastasis. Flocks performed cystectomy for this disease in 1946, and the patient was reported well seven years later. Admittedly, two favorable results are few in number, but they comprise a large proportion of the patients treated by cystectomy and contrast strongly with the complete failure of other reported methods. It should be noted also that Flocks' patient and mine were suffering from postoperative recurrences at the time of cystectomy. It seems reasonable to believe that cystectomy performed as the initial treatment should be even more successful.

TUMORS OF THE PROSTATE

About 100 tumors of the prostate have been described in infants. All were sarcomas.

Symptoms

The symptoms are those of progressive obstruction of the bladder outlet with greater and greater straining to void until violent contraction of all accessory muscles fails to express even a spurt of urine, and retention is complete. Hematuria is unusual because ulceration is uncommon, and infection occurs relatively late in the course of the disease.

Diagnosis

Diagnosis of bladder obstruction by a prostatic enlargement is not difficult because rectal examination reveals a prostate of considerable size. Catheterization shows an elongated posterior urethra, and, in excretion urograms, massive intrusion of the prostate into the bladder is visible. However, it is difficult to recognize the nature of the growth without incising it, because the tumor is soft in consistency, suggestive of an abscess, and aspiration biopsies, at least in my experience, usually fail to show the true condition.

Treatment

Treatment of prostatic sarcomas in infants, to be successful, must be early and adequate. This statement expresses a goal yet to be achieved. Certainly all operations short of removing the bladder and prostate have failed, and I have never observed any benefit following interstitial or external irradiation. A few attempts have been made to remove these tumors with extensive operations; in some the immediate results were good, but recurrences followed. It is likely that successful treatment of these tumors always will present great difficulties because incision of the growth facilitates its rapid extension, and removing it in toto is prevented by its friability.

TUMORS OF THE TESTIS

Tumors of the testicle in infancy are rare. Gilbert, in a study of 5500 testis tumors collected from the literature, found only 131 appearing before the age of 15 years. Campbell[1] remarks that these tumors in the young are predominantly an affliction of the first three years of life and that their possible occurrence at birth and occasional bilateral incidence reflect their congenital origin.

Symptoms

With few exceptions, the first and the only symptom of a testis tumor is an enlargement observed by the patient's mother. It is helpful that mothers are quick to investigate any real or fancied genital abnormality in their boy babies. On the other hand, increase in size is an exceedingly crude measure of the possible extent of the disease, because tumors of different types metastasize after varying periods of growth and not infrequently before significant enlargement has occurred. Though early discovery of a testis tumor in an adult is none too frequent, it is facilitated by the patient's ability to feel a small hard nodule, especially after his attention has been attracted to the region by a trauma or a drag on the spermatic cord. He may then seek medical advice. The infants' testis usually is too small for one to feel within it an area of increased density, it is rarely traumatized, and it seldom exerts painful traction on the cord. Therefore discovery of the disease before metastasis occurs depends almost entirely on early recognition of the true nature of a moderate swelling.

Diagnosis

Except for the local condition, the infant appears normal. Inspection shows enlargement, usually in one side of the scrotum, with no redness of the skin suggesting inflammation unless heat has been applied. If the tumor is large, the scrotal skin may be stretched and shine, but usually the normal rugae are present. As in the adult, the first consideration in palpating the enlargement must be to demonstrate the source of the swelling to be in the testis rather than in the epididymis. This is seldom difficult in the infant, because the epididymis is small and epididymo-orchitis rarely occurs. The spermatic cord is normal. The tumor, whatever its size, retains the shape of a normal testis because of the tensile strength of the tunica albuginea. The tumor is dense and, as a result, heavy. These characteristics are pathognomonic of a testis tumor. While palpation must be gentle in order to avoid disseminating the disease, local tenderness seldom is elicited.

Occasionally the tumor is surrounded by fluid which prevents accurate palpation. This can be removed safely by aspiration as long as the tunica albuginea is not punctured. Commonly this fluid is clear and amber-colored. If it is grossly bloody, it suggests that the growth has invaded the epididymis, because all of the testis is covered with impermeable tunica albuginea. The growth does not transmit light. It is advisable to do a serologic test for syphilis, because a patient with a gumma of the testis almost invariably has a strongly positive reaction. In infants this is rare.

After investigation of the scrotal contents the abdomen, especially

of the same side, should be palpated for metastases. If present, they are most likely to be felt as a large, round, firm retroperitoneal mass growing in the region of the renal hilum. The breasts should be examined for gynecomastia, a bad prognostic sign because it indicates that the tumor is of trophoblastic origin. Finally, the left supraclavicular fossa should be searched for a characteristic signal node.

Excretion urograms should be made to show possible distortion of the ureters by metastatic iliac or periaortic lymph nodes, and a chest film should be taken in search of blood-borne metastases. These appear as dense spheres of various sizes. No matter how large they may become, they always retain the round shape of the vein lumen in which their growth began.

Diagnostic steps should be carried no further. No diagnostic measures should be performed in the operating room. A solid testicular enlargement never should be incised to obtain material for a microscopic examination. This ill chosen maneuver with a tumor is invariably followed by rapid fungation. If any diagnostic errors are made, let them be made on the side of the patient's safety. If care is used, such errors will be few and loss to the patient will be insignificant, because any condition which produces a solid swelling of the testis simulating a tumor also destroys its spermatogenic function.

Treatment

After examining the pathologic descriptions of old case reports of testis tumors in infants, a urologist is inclined to believe that these growths are quite different from testis tumors in adults because so few of them seem to fit into accepted modern classifications. Probably this is only a difference in terminology and is not due to fundamental structural differences in testis tumors of different age groups. Although I know of no classifications of testis tumors in infants, in my personal experience they have had a similar natural history to testis tumors in adults, and their structure has been similarly described by modern pathologists. However, in infants testis tumors may show a larger proportion of embryonal types. At any rate, I believe that until contrary evidence develops, and none now exists, testis tumors in infants should be treated in the same general way as those in adults.

As soon as the clinical diagnosis has been made, the tumor should be removed with the spermatic cord doubly ligated and severed at the internal abdominal inguinal ring. An important reason for this operation is to obtain the primary tumor for careful microscopic study, upon which subsequent treatment will be based. It will be noted that even if metastases are present, removal of the testis tumor is advisable in

order that the radiosensitivity of the growth may be estimated as nearly as possible on the basis of its structure.

When no metastases have been found and the tumor is a seminoma, a highly radiosensitive neoplasm, irradiation only should follow orchiectomy, and a tumor dose of 2000 roentgens delivered in about six weeks should be given the lymphatic routes draining the testis from the inguinal region to the epigastrium, inclusive. Three anterior and two posterior portals suffice. The 250-kilovolt unit is sufficiently powerful for young children at a target skin distance of 70 cm.

If the tumor is a choriocarcinoma, no radiation is given, because this growth is radioresistant and spreads most frequently through the blood stream.

If the tumor is a relatively resistant embryonal adenocarcinoma, a teratocarcinoma or an adult teratoma, the lymphatics should be carefully dissected from the diaphragm to the internal abdominal inguinal ring. All lymphatics and nodes which can be removed should be carefully resected with the surrounding fat, and wherever any enlarged nodes are discovered a few metal skin clips should be fixed to direct subsequent irradiation more accurately. Such a thorough lymphatic dissection can be performed only through an adequate approach. This requires either the Nagamatsu or the thoraco-abdominal incision. The common lumbar approach to the kidney is inadequate.

Three or four days after surgical removal of the lymphatics, whether or not metastases were found, irradiation should be given using the five abdominal portals already mentioned. If possible, a tumor dose of 3000 roentgens should be delivered between the groin and epigastrium, inclusive. While a larger tumor dose probably would be more suitable for metastases from teratocarcinomas, embryonal adenocarcinomas or adult teratomas, 3000 roentgens is about all the infant can tolerate. It is impossible to prescribe the time required for applying a specified amount of radiation to an infant, because the daily doses depend on the tolerance of the individual, and, as a group, infants are relatively intolerant as compared with adults. One can start with a daily dose of 200 roentgens and reduce it if necessary. Generally speaking, the period of treatment should be as short as possible. During treatment the infant should be observed closely, blood cell counts should be performed at intervals of three or four days, and, if the white blood cells fall significantly, transfusions of whole blood appropriate in quantity to the size of the infant should be given.

If metastases are demonstrable at the time the tumor is recognized, particularly if the lungs have become invaded, radiation alone should be used to give as much palliation as possible. Treatment should be directed to the regions affected and continued aggressively as long as it is beneficial. The results will depend on the radiosensitivity of

the growth and its extent. In general, an encouraging proportion of infants with testis tumors should be cured. Here again, success depends on early diagnosis and prompt application of appropriate treatment.

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CALCULOUS DISEASE IN INFANTS AND CHILDREN

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Calculous disease in children is not the most frequent urologic problem occurring in this age group. It is, however, encountered often enough so that the diagnosis must be considered in problem cases and as a complication of other, more frequently occurring pediatric illnesses.

In children, age appears to play little if any role in the occurrence of urinary calculi. Stones have been reported in all ages from six months to ten years with equal frequency. Sex likewise in this group has not been found to be an important factor.

Urinary stasis and infection definitely play an important role and account for the great percentage of calculi which ultimately present themselves for definitive treatment.

There is no statistical evidence available to indicate the number of cases in which symptoms are actually produced by urinary tract calculi which are relieved spontaneously.

The difficulty with which the diagnosis is usually made can be appreciated when one considers that from one third to one half of all urinary stones in infants and children are uric acid or urates. This crystalline structure is nonopaque to x-ray or at best very poorly visualized. The frequency with which uric acid infarcts have been demonstrated in the kidneys of infants and children would tend to support this clinical finding. It has been estimated that these lesions could be found in 100 per cent of kidneys by the age of eight or nine years. It is the impression of many urologists that a definite percentage of abdominal colicky

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episodes seen in the earlier ages are actually due to the passage of small clusters of uric acid crystals. If gross hematuria should occur under these conditions, more often than not it is attributed to one of the manifestations of glomerulonephritis rather than urolithiasis.

TYPES OF STONE

The various crystalline compositions of calculi found in infancy and childhood are essentially the same as those found in adults. As previously mentioned, 30 to 50 per cent of stones are urates or uric acid. A small percentage are cystine, the result of a metabolic deficiency which allows the urinary excretion of cystine. The remaining ones are calcium oxalate or calcium magnesium phosphate. These latter types are found in conjunction with urinary tract obstruction, with or without infection. Oxalate stones are more apt to occur without infection, while phosphatic stones are likely to be found with urosepsis, especially if a urea-splitting organism is present.

ETIOLOGY

In the presence of obstruction, stasis and infection, it is not difficult to account for the formation of calculi on a simple physical basis. A nidus is formed from a clump of epithelial cells or bacteria. In the presence of an alteration of *p*H, supersaturation of the solution and a disturbance of the urinary colloid, precipitation of crystalloid material is initiated on the nidus. It is further enhanced by these factors deviating from the normal equilibrium and following strict physicochemical processes. In this connection Higgins[7] and others have pointed out that deficiency of vitamin A leads to hyperkeratinization of the urothelium, increased formation of potential stone nuclei and urolithiasis. Subsequent investigation has not completely confirmed the original theories, but the reports of Brown[4] suggest that this factor may be more important in urolithiasis in children compared to adults.

The etiology of calculi which form in the absence of other urinary tract pathology does not lend itself as easily to explanation. Burkland[5] has uniquely proposed that urolithiasis of this category might be explained by a temporary or permanent derangement of normal metabolic processes which influences crystalloid excretion. Further clinical and biochemical investigation will be needed to support this theory.

SYMPTOMS AND DIAGNOSIS

Renal Calculi

The diagnosis of urinary tract calculi in children is seldom a primary one except in an occasional and typical case of bladder stone. Abdom-

inal pain, backache, nausea and vomiting, diarrhea, anorexia, fever and convulsions may be symptoms of urolithiasis (Fig. 71). These symptoms also occur with other, more common conditions of children, and the urinary tract is seldom, if ever, in the first order of suspicion. Gross hematuria requires complete urologic investigation except in cases of clear-cut glomerulonephritis. Persistent pyuria and any voiding irregularities should also fall in the same classification. Finally, children who have shown some or all of these symptoms, and in whom investigation of other systems has failed to disclose a cause, should have the benefit

Fig. 71. Plain roentgenogram of a 12 months old boy, showing a right renal calculus. Child had gastrointestinal symptoms since birth. The stone was found incidental to an intestinal barium study. Urinalysis then revealed a marked pyuria. Stone removed by pyelolithotomy.

of a urologic study. This should be done even though nothing points directly to the urinary tract. Not infrequently, serious urologic disease with or without stones is reflected as dysfunction of other systems, particularly the gastrointestinal tract.

Unfortunately for many children with calculous disease, 40 to 60 per cent of stones are of the so-called silent type—present without overt symptoms. This occurs more frequently in children than in adults, and is usually associated with some condition which prevents the stone from moving. When such a stone develops in the kidney, the usual life history is a gradual steady increase in size by the accretion of additional crystals. This increase proceeds at varying rates with different persons, but without the intervention of treatment the ultimate outcome is total destruction of the kidney.

The reason why a stone developing in a kidney fails to move is usually that there is an obstruction in the upper urinary tract or a firm

attachment to the pelvic epithelium. In the absence of painful symptoms directing attention to the urinary tract, the commonest finding in these cases is a persistent or recurrent pyuria. If, when these conditions obtain, a complete urologic study be carried out, the calculous as well as any associated urologic pathology would be discovered. The application of the proper treatment at the earliest possible time would save many more kidneys than are being salvaged at present.

Ureteral Calculi

Ureteral calculi are less likely to be of the "silent" type, unless there is extensive dilatation of the upper urinary tract—hydronephrosis and

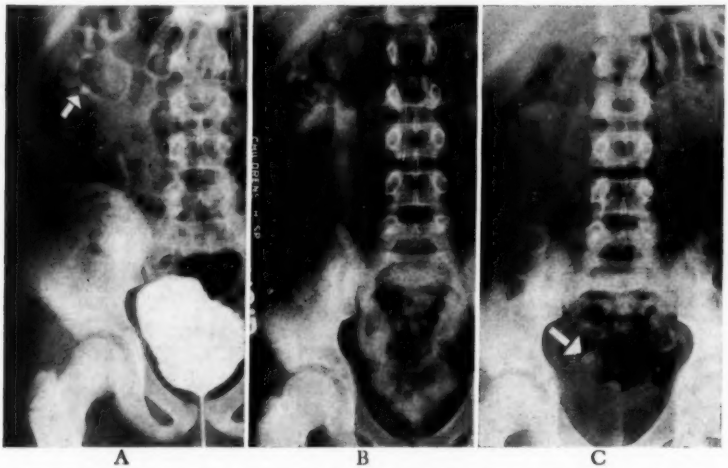

Fig. 72. Silent stone in a 7 year old boy with congenital hydronephrosis and hydroureter. Calculus migrates back and forth between inferior dilated calyx and lower end of ureter. *A*, Stone in calyx. *B*, Pyelogram showing dilatation of the upper urinary tract. *C*, Stone in lower end of ureter. Operation refused.

hydroureter (Fig. 72). Stones up to 2 mm. in size will ordinarily pass even through the ureter of an infant. Larger calculi, particularly if spiculated, will encounter difficulty at the ureteropelvic or ureterovesical areas. As to the probability of spontaneous passage of a ureteral stone, it has been estimated that passage will occur if the diameter of the calculus in millimeters measures no more than one third the child's age.[6] This, however, can be dangerous if insufficient weight is given to other factors, i.e., infection, hydronephrosis and renal damage (Fig. 73).

Fig. 73.

Fig. 74.

Fig. 73. One hour delayed excretory urogram of an 8 year old girl, showing ureteral calculus obstructing the left pelvic ureter. Child had flank pain and gastrointestinal symptoms for 3 months. Stone removed by ureterolithotomy, but infection persisted for many months.

Fig. 74. Large calcium oxalate bladder calculus in a 7 year old boy. Patient had neurogenic bladder dysfunction following poliomyelitis, as well as congenital multiple arthrogryposis. Urine was practically sterile, and mild symptoms present for only 2 weeks. Stone removed by suprapubic cystotomy.

Bladder Calculi

In order of incidence, bladder calculi rank below stones in the upper urinary tract. Their occurrence is practically always secondary to obstruction of the bladder outlet, neurogenic dysfunction of the bladder, or as a sequel of catheter drainage for a long time. Catheter drainage and either of the other conditions frequently exist together. The role that catheter drainage plays in the etiology of vesical calculus develops from the fact that phosphatic encrustations tend to occur on the ends of such tubes and may easily be dislodged when these tubes are changed. This provides an ideal nucleus upon which further aggregations of crystals may deposit. Such bladders should be thoroughly irrigated to remove any crystalline particles whenever catheters are changed.

Vesical calculi which develop secondary to congenital bladder neck obstruction occur somewhat more often in males than in females because the bladder neck obstruction is usually more severe in this sex.

The symptoms which accompany bladder stone, when they occur, are more typical than for stones occurring at any other site in the urinary tract. Symptoms most frequently occur with the child in the erect position and toward the end of urination. The rationale for this is

that the most severe symptoms develop from the stone making contact with the trigone, which is the most sensitive portion of the bladder. Both the erect position and the final contraction of the detrusor facilitate the advance of a freely moving stone from the more insensitive bladder floor to the trigone, initiating the typical "fit of stone."

Conversely, symptoms are often relieved by lying down, thereby allowing the stone to roll back into the bladder cavity and away from the trigone. These children will exhibit a sudden, excruciatingly painful interruption of the urinary stream caused by the ball-valve action of the stone being forced across the bladder outlet. This is associated with tenesmus and pain referred to the external genitalia. They will squeeze, pull or otherwise manipulate the external genitalia, either because the symptoms appear to be in this area or because of a subconscious desire to impede the outflow of urine, which is associated with marked discomfort. With such symptoms present over a period of time, they will discover unusual voiding attitudes or patterns which, by trial and error, they find will minimize or relieve these distressing manifestations. Not uncommonly, such children are indicted as masturbators and submitted for psychiatric treatment or unjustly punished.

Bladder calculus should also be considered when children have hemorrhoids or rectal prolapse and in boys when priapism occurs with pathologic frequency. The former conditions develop as a result of tenesmus and straining to urinate. The latter is a reflex neurogenic mechanism initiated by irritation of the trigone and bladder neck from the calculus impinging on these areas.

Vesical calculi developing in connection with neuromuscular dysfunction of the bladder are not as likely to show the typical bladder spasm symptoms (Fig. 74). They often lack the normal sensory nerve supply or pathways, as well as the motor limb of the reflex arc. Varying amounts of residual urine are retained by these children up to elimination by overflow alone. This naturally favors stone formation, but at the same time eliminates the mechanism for the production of symptoms. Bladder stones in these cases are usually discovered incidental to other x-ray examinations or when a survey of the urinary tract is demanded by infection or bleeding.

A rare complication of bladder stone has been reported[6] in which erosion and rupture of the bladder can occur with extrusion of the calculus into the perivesical space. In girls a vesicovaginal fistula can form with the stone passing into the vagina.

IMMOBILITY AND CALCULI

The role of recumbency and immobilization in stone formation is worthy of mention. It has been a clinical observation for many years

that such conditions favor calculus formation in the urinary tract. Excluding pre-existing pathology of the renal system, there are two principal alterations which appear to have the main influence.

First, recumbency produces a certain amount of urinary stasis, the action of which has already been noted. Secondly, immobilization causes a decalcification of the bones, producing a physiologic hypercalcinuria. The excess calcium excretion begins soon after immobilization and continues for one to two months, depending on the activity. About this time equilibrium occurs, or the excretion may be slightly less than normal for a short time. From a urologic viewpoint the dangerous time for stone formation is during the period of excessive calcium excretion. It is interesting to note that mobility, even passive mobilization, decreases the amount and shortens the interval of hypercalcinuria. The stress of activity profoundly influences the retention of calcium in the skeletal system. Prophylactic management in cases of this type, therefore, should include mobilization, active or passive, so far as possible, adequate hydration, acidification of the urine, treatment of any urinary infection and guarding against any abnormal dietary intake of calcium.

NEPHROCALCINOSIS

Since allusion has been made to the influences of abnormal calcium metabolism and its relationship to stone formation, consideration must be given to a group of pathologic or otherwise altered physiologic states, one reflection of which may be calcifications in the urinary tract.

When these calcifications become apparent, the condition is referred to as nephrocalcinosis, regardless of the underlying physiologic derangement. The most widely known condition associated with nephrocalcinosis is hyperparathyroidism, but other, lesser known conditions include Cushing's disease, hypervitaminosis D, the administration of cortisone, an occasional pituitary disturbance, certain nephrotic changes associated with high intestinal obstruction or pyloric stenosis, an occasional infection, and idiopathic hypercalcinuria. All these conditions are associated with a general disturbance of calcium metabolism usually ending in hyperexcretion. In addition, there often can be demonstrated some renal tubular damage or deficiency.

As an example, nephrocalcinosis and lithiasis occurs in nearly 100 per cent of cases of tubular acidosis. In this condition the renal tubule is unable to form ammonia, in consequence of which the normal alkali reserve is depleted and calcium is mobilized to maintain acid-base balance. In known parathyroid disease only about 30 per cent of patients exhibit nephrocalcinosis in the presence of hypercalcinuria. It might be said that urolithiasis is more likely to occur in hypercalcinuria

if the integrity of the tubule is preserved, and nephrocalcinosis will result when tubular damage is present.

Diffuse renal calcification has been observed after recovery from mercury bichloride intoxication. Here, however, there is tubular damage and a demonstrated local, rather than general, hypercalcemia. The calcium is deposited as a part of the healing process in the degenerating and necrotic tissue.

Anderson's[2] report of nephrocalcinosis in 20 autopsy cases in infants and children reveals it to occur in association with a variety of conditions. Evidence of renal tubular damage clinically and microscopically was invariably found. Four of the cases had received parathyroid extract and calcium salts. Other factors of clinical importance in these cases were infection, intestinal obstruction, dehydration and acidosis.

The recent work of Baker, Reaven and Sawyer[3] on experimental nephrocalcinosis has indicated that the state of the connective tissue ground substance is intimately concerned in the determination of whether calcification will take place and to what degree. Several methods of altering the connective tissue matrix were applied, and incontrovertible evidence was presented to show changes in the ability of the tissue to undergo calcification. These data would tend to support the proposal made by Anderson and McDonald[1] that renal calcification and lithiasis is a systemic or dietary disease rather than a disease of the kidney per se.

TREATMENT

The treatment of urolithiasis, regardless of age, is so varied as to defy adequate or complete description. So many factors must be considered that each individual case is a problem unto itself, and no two cases are exactly alike in all respects. Dogmatic statements about management of urinary calculi should be viewed with some misgivings. In general, the principal objectives of treatment are the relief of pain, the prevention of progressive renal damage, and the elimination of infection. The conservation of renal substance in infants and children is often of greater relative importance than in adults, because the congenital defects of the urinary tract are so frequently bilateral. The general classification of treatment is somewhat confusing, but is usually divided as surgical, or radical, versus nonoperative, or conservative. Surgical treatment, however, is sometimes referred to as conservative, in this case connoting conservation of renal substance.

Surgical Management

With present methods available for anesthesia, correction of anemia, establishment of favorable nitrogen balance, intravenous fluids and

antibiotics, many cases now can have the benefit of surgical therapy, which would have posed too great a risk a few years ago. Age alone is no longer a serious consideration. Infants and children with proper preoperative and postoperative care tolerate urologic surgery even better than do adults.

It should be a foregone conclusion that a complete evaluation of the entire urinary tract be at hand before any treatment is advised. This means not only an anatomic, but also a physiologic status of all parts necessitated by the frequent concomitant existence in children of obstructive lesions with the calculous disease. Treatment in these cases involves not only removal of the calculus, but correction of the obstruction as well.

Contraindications. Contraindication for operative treatment of urolithiasis in children most often arises for some reason outside the urinary tract. Severe cardiopathy which precludes the stress of surgery, disease with a hopeless outlook such as leukemia or other incurable neoplasia, and some blood dyscrasias with severe bleeding tendencies, such as hemophilia, are a few worthy of mention. Yet under certain circumstances even these may not be absolute contraindications.

Indications. It could be stated that any child who has a renal stone too large to pass is a potential surgical candidate. Such surgery should also be carried out as early as feasible because the risk of renal damage outweighs that of operation and the result is more satisfactory. It is a general impression that children will develop a chronic nonresponsive pyelonephritis more quickly than an adult under the same set of circumstances and at the same time appear clinically to tolerate such infection better.

Not all stone-bearing kidneys can or should be preserved. If the renal parenchyma has been almost completely destroyed by a large calculus or associated infection, and the other kidney is normal, it should be sacrificed. An organ incapable of contributing 20 per cent or more of total renal function cannot support life if the normal kidney is lost, and little would be gained for longevity by its salvage. It has also been observed that removal of such a kidney decreases the chance of stone developing in the sound mate.

Bilateral renal disease is considerably more complicated in treatment. The location of stones, presence of obstruction, type of infection, and the functioning capacity of each side must be carefully determined and judged before a program of treatment is begun. Usually the poorer of the two sides is attacked first so that it will have a longer recovery period and be subjected to the stimulation of increased work while the second side is being treated. It has been shown that the degree of recovery will definitely be greater than if such stimulation is lacking.

Procedures. For renal pelvic stones simple *pyelotomy* usually suffices.

Calyceal stones can sometimes be extracted through a pyelotomy incision, but if the infundibulum is too narrow for this maneuver, a small nephrotomy incision is generally adequate. A combination of both incisions is frequently used in handling branched calculi which are not too large. For the large stag-horn type of calculus an extensive nephrotomy incision is required. The kidney is almost bivalved along the convex border, the stone removed, and the renal substance coapted carefully with bolster-type sutures. Hemorrhage becomes an increasing problem the more extensive the incision made.

In some cases in which stone develops in a calyx or extends into this area from a pelvic stone the epithelium may be irreparably damaged, and recurrent stone formation will be an obvious sequel. Under such circumstances it is better to remove this portion by *calycectomy*. If the parenchymal damage is still more extensive, but limited to either the upper or lower pole, the situation may lend itself to heminephrectomy, preserving what may amount to be a fairly respectable kidney. The hallmark of all these surgical procedures is salvage of renal substance whenever possible.

As an adjunct to the more complicated surgical procedures, *nephrostomy drainage* may be indicated for a time postoperatively. This may be particularly true if it has been impossible to remove all small stone fragments. In the postoperative period these fragments may be dissolved or dislodged by irrigation through the nephrostomy tube with one of the solvent solutions such as Solution G.[7] In children particularly, it is wise to discontinue artificial tube drainage as soon as possible, because the associated foreign body reaction and superinfection appear to be more marked than in adults.

Ureteral calculi in children are handled most often by *ureterolithotomy*, when the need for active treatment arises. As mentioned proviously, expectant treatment—waiting for spontaneous passage—should be advised guardedly. The child should have the benefit of close observation, and at the first signs of obstruction, renal pain, fever, pyuria or dilatation above the stone on x-ray examination, prompt surgical removal is indicated. The variety of urologic instruments available for the manipulative extraction of ureteral calculi in adults is not applicable in children. Anatomically, the parts are too small to use these instruments with any degree of safety. However, in children 10 to 15 years of age one device is worthy of consideration. This is the loop catheter. It can be introduced through a small instrument and with proper care might occasionally find a place in the armamentarium of therapy.

Bladder stones most frequently present themselves as a surgical problem. The reason, of course, is the high frequency of concurrent obstructive uropathy at the bladder neck requiring surgical correction. Removal

of one without the other would be inadequate treatment. Crushing procedures—*lithalotripsy*—have limited application in children, mainly because the caliber of the urethra precludes the passage of the standard lithalotrite. In an occasional case in which a large suprapubic tube is already present, such manipulations may be carried out through the suprapubic sinus. However, the procedure should not be attempted on calculi larger than 2 cm. in diameter, when stones are multiple, or if the composition is chiefly oxalates, which are extremely hard.

Medical Management

Except for two specific instances, the medical, or nonoperative, management of urolithiasis is concerned with the prevention of recurrent stone or stopping the growth of an existing calculus not amenable to surgery. Seldom is it the primary mode of therapy, but as an adjunct to surgical treatment some facet will find an application in almost every case. The two exceptions just mentioned are the cases of pure uric acid and cystine urolithiasis.

In connection with all urolithiasis, but in particular the medical management, the importance of an analysis of the stone is obvious. Newer methods of crystallographic analysis are in the process of experimentation, but even at present an accurate chemical analysis of all calculi should be carried out to form a basis for sound medical therapy. Such therapy consists in an attempt to alter the excretion of that type of salt or ion which formed the stone, or to alter the physicochemical status of the urine to keep such salts in solution or suspension.

Uric acid and cystine calculi form in acid urine but not in alkaline. Keeping the urine at a *p*H of 7.5, with sodium bicarbonate or sodium citrate, will prevent precipitation and even cause dissolution of stones already formed.

Producing an alteration in calcium excretion in connection with recurrent calcium-containing stones is not as simple a problem. Some factors are worthy of mention. Calcium phosphate is more soluble in acid urine, approximately eight times more soluble at *p*H 5 than at *p*H 8. Acidification is therefore an important factor. However, in some urinary infections with urea-splitting organisms it is impossible to convert the urine to the acid side of the scale. In this circumstance attempts at acidification by acid ash diet or ammonium chloride might even prove disastrous. Such therapy over a period of time causes more calcium to be released from bone and excreted into an already supersaturated alkaline urine, and enhances calculus formation. Acidification with sodium acid phosphate has been shown to circumvent this process.

Limitation of calcium intake, while not a grave problem in adults,

is of considerable importance in infants and children. By far the highest amounts of calcium come from dairy products, which can be eliminated by the former, but involves unusual dietary management for the latter.

By all odds the simplest and yet a very effective method of influencing crystalline precipitation is by dilution. Increasing the urinary volume decreases the concentration of salts present for stone formation. This is perhaps the only effective means against the formation of oxalate stones, although a low oxalate diet is generally advised.

Urinary Colloid

In recent years the role of protective urinary colloid has been under investigation by A. J. Butt[7] et al. There is evidence to show that in normal urine ultramicroscopic particles of crystalline material are coated with a colloidal substance which prevents this crystalline material from aggregating. In stone-forming subjects this colloid is absent, and clumping of the crystalloid material is found. Butt also found that the subcutaneous injection of the enzyme hyaluronidase restores protective colloid to the urine of such persons and prevents recurrence of calculi, regardless of composition, in children as well as adults. The enzyme acts on the ground substance of the subcutaneous tissue, the degradation products appearing in the urine as protective colloid. Such treatment, while not a panacea for urolithiasis, appears to have a place as adjunctive therapy.

Clinical trial has revealed several limitations. In the presence of infection its value decreases rapidly, for it appears that the bacteria destroy the colloid as it is found in the urine. In certain cases under treatment, using too small a dosage has produced a sensitization reaction, which has caused stones to increase more rapidly than would normally be expected. A definite contraindication to its use is renal impairment. In such cases under the influence of hyaluronidase therapy, calculi have formed more rapidly than would be anticipated. At present there is still no clear-cut regimen for dosage or for the selection of cases in which this therapy is indicated.

SUMMARY

Calculous disease in infants and children occurs frequently enough to be included in the differential diagnosis of many atypical childhood illnesses. Persistent pyuria is the most common clinical finding, and demands complete urologic investigation. Urinary stones in this age group are more often associated with obstructive uropathy than in adults.

Renal tubular damage is an essential factor in addition to hypercalcemia and hypercalcinuria for the development of nephrocalcinosis.

The treatment of urolithiasis in children should be early and vigorous. Parenchymal salvage is of paramount importance for these patients for long life expectancy. Primary therapy is usually surgical, but medical management is adjunctive and directed against recurrences.

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DEVELOPMENTAL RETARDATION DUE TO UROLOGIC DISEASE

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Discussion of developmental retardation in this paper will be limited to consideration of intrinsic problems of the urinary tract as reflected in growth failure.

Investigation of growth failure should always include an evaluation of the genitourinary tract and its function, unless some obvious defect of the endocrine, metabolic, cardiovascular, gastrointestinal or central nervous system is clearly demonstrated. Genitourinary tract disease sufficient to create developmental retardation may be due to congenital defects with or without infection in the tract. Acute infections of the urinary tract, such as single episodes of cystitis or pyelitis, usually do not create a growth failure problem. The adaptive mechanism of the pediatric patient in recuperating from a single acute infection is great enough to prevent a prolonged interference in metabolism and a subsequent growth failure. However, if acute urinary tract infections are repetitive and not adequately treated, malnutrition may develop.

GROWTH FAILURE DUE TO CONGENITAL ANOMALIES

The presence of an underlying congenital defect in the urinary system always must be ruled out if infections occur beyond a second episode. Some congenital defects may create growth problems from earliest infancy, but many are compatible with good health until childhood or adult life, when superimposed infections bring about investigations uncovering the defect.

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Urinary tract congenital anomalies may be divided into two groups of lesions:

I. Lesions obstructing urinary flow
   A. Those involving the urethra or bladder neck
   B. Those involving the ureterovesical junction, ureters or renal pelvis
   C. Neuromuscular dysfunction
II. Lesions not obstructing urinary flow

The malformations of group I are the most common lesions and include such anatomic anomalies as posterior urethral valves, vesical neck contracture, absence of one or both ureters, duplication of ureters, ectopic ureters, and aberrant blood vessels causing extrinsic compression of ureters. Under the subgroup of lesions noted as neuromuscular dysfunction may be considered the megaloureters of unknown etiology and the atonic ureters and bladder associated with abdominal muscular weakness, as seen in poliomyelitis, and the neurogenic bladder of spinal cord disease.

Lesions not obstructing the urinary flow include exstrophy of the bladder, congenital cystic kidneys and hypoplasia of the kidneys. Marked growth failure with renal insufficiency and death in uremia and acidosis is seen in bilateral hypoplasia of the kidneys. If the hypoplasia is unilateral and the normal kidney has good function, removal of the hypoplastic kidney should be done. Usually the prognosis is good in this situation if infection does not occur in the remaining kidney. Growth failure is uncommonly seen in exstrophy of the bladder unless infection occurs in the urinary tract. If there is extensive involvement of both kidneys in polycystic disease, renal insufficiency with progressive uremia and poor physical development may result in death in early infancy. Polycystic disease of the kidneys may be compatible with life through adulthood without growth failure and may not be recognized until the fourth or fifth decade of life.

There is no adequate explanation for the growth failure seen in urologic disease. Usually in the presence of azotemia and renal acidosis, one thinks of the altered calcium metabolism with excess loss of calcium through the kidneys as the contributing factor. However, as more information is being obtained on the urinary excretion of amino acids and other metabolites, it is within the realm of good reasoning to think that factors other than calcium loss contribute to growth failure. In pediatric practice, as we shall try to demonstrate clearly by a case report, it is not at all uncommon to find growth failure in the absence of azotemia and renal acidosis. Growth failure will occur in the presence of any chronic disease, be it urologic, pulmonic, cardiac or neurologic. An adequate explanation for physical retardation in the chronically "sick child" must yet be found.

CLINICAL APPROACH TO THE PROBLEM

Many growth failure problems may present themselves to the clinician without any symptoms directly related to the urinary tract. The *history*, as given by the parents, is usually characterized by anorexia, abdominal pain, occasional vomiting, irritability, slow gain in weight, and occasionally difficulty in voiding. *Physical examination* reveals varying degrees of malnutrition, pallor and irritability. Other findings may include frank dwarfism, poor skin turgor, hypertension. If a hydronephrosis, hydroureter, or large bladder due to obstruction is present, the abdominal examination may reward the clinician with the palpation of an "abdominal tumor," which may disappear when the patient voids. Abdominal palpation may be enhanced under anesthesia or sedation.

Urinalysis may indicate the presence of albumin of mild to moderate degree, some pus cells and perhaps red blood cells. Urine culture usually yields the organism of the infection. Many times the urinalysis may be entirely normal unless done during a febrile episode. It is best to use a catheterized urine specimen for these studies in the female child. A clean voided specimen is adequate in the male child. Frequently an elevated blood urea determination may be the only initial positive laboratory finding.

Intravenous *urography* is indicated in any patient who has had more than two well authenticated urinary tract infections or in any patient in the pediatric age group who displays growth failure, even in the absence of demonstrable infection. Residual urine determinations are important in evaluating the clinical impression of dribbling, dysuria or difficulty in voiding. Quantities of more than 10 cc. of urine repeatedly obtained as residual in the bladder should suggest the possibility of bladder neck obstruction.

Further investigations, such as *cystoscopy, cystograms, retrograde pyelograms*, may be clearly indicated in determining the extent of urinary tract inadequacy. These procedures not only aid in establishing anatomic defects or abnormalities, but also permit the investigator to determine the presence of infection in each ureter and kidney and to determine the output of each kidney. In the infant and child these procedures should be performed under general anesthesia. *Aortograms* may be very helpful in establishing such diagnoses as unilateral or bilateral hypoplasia of the kidneys.

Treatment, once the diagnosis is established, may be variably successful. Since many of the anomalies, such as duplex kidneys, may be compatible with long life unless infection is present, vigorous treatment of infections is indicated. When infection is controlled by the appropriate antibiotic agent as determined by sensitivity studies, it is well to continue constant and prolonged therapy for months, and perhaps years, with an oral medication in order to prevent recurrences. Usually

one of the sulfonamides or Gantrisin may be used for the prolonged therapy in doses of 0.5 to 1.0 gm. daily. Too often, urinary tract infections are treated in a short-term manner, and recurrences are common.

Those lesions creating an obstruction to urinary flow should be attacked surgically. Vigorous therapy for control of infection should accompany the surgical correction. This may call for the combined efforts and cooperation of the urologist and the pediatrician. When renal insufficiency, azotemia and renal acidosis are present, intravenous therapy and correction of electrolytes is of great importance, in addition to the surgeon's skill and the supportive control of infection.

CASE REPORTS

The following case report is presented as an example of the effect on a growth curve of a urinary congenital anomaly with superimposed infection without renal failure, which was difficult to prove clinically for several months after birth.

CASE I. J.M., a female infant born April 21, 1951, was the product of an uneventful pregnancy and delivery. Her birth weight was 6 pounds 10 ounces, her birth length 19 inches. Her developmental history and routine physical examinations were normal except for only fair weight gain and a mild degree of malnutrition. Repeated urinalyses and blood counts were within normal limits. Her growth pattern outlined on the Wetzel grid is shown in Figure 75. At 2 years of age, in April, 1953, she had an unexplained febrile episode. Thereafter, until September, 1953, she had 2 more unexplained febrile episodes each of 2 days' duration. Urinalysis in August, 1953, was normal. During a bout of high fever in October, 1953, a catheterized urine specimen revealed a few pus cells and yielded an *Escherichia coli* on culture. The patient's blood chemistries were normal. An intravenous urogram revealed the presence of bilateral duplex kidneys and duplex ureters with caliectasis of the lower pole of each kidney, suggestive of infection. On the Wetzel grid her persistent growth failure until the diagnosis of urologic disease was made is noted through the sign "N."

Antibiotic therapy and chemotherapy, using Aureomycin, Gantrisin or Furadantin, were given daily for the succeeding 14 months. There was much improvement in her growth curve, as noted on the Wetzel grid by the sign "O." A repeat urogram, cystogram and retrograde pyelogram, obtained 8 months after initiation of therapy, were normal except for the presence of the bilateral duplex kidneys and ureters. Evidence of infection was absent. At the time of this writing she has remained free of genitourinary tract infection and is doing well with a constant normal growth pattern. Her congenital anomaly is compatible with life and good health, provided superimposed infections can be prevented.

The following history illustrates the existence of a congenital anomaly of such severe degree that it had created a situation incompatible with life beyond a few months.

CASE II. R.C., a male infant, was born June 3, 1953, to a gravida I mother who had toxemia the last trimester of pregnancy. The labor and delivery were normal. The baby's birth weight was 6 pounds 15 ounces. His neonatal history was characterized by vomiting, polydipsia and slow weight gain. At 4 months of age his weight was 15 pounds, and at 6 months of age it was 12 pounds 6 ounces.

He was seen here at 6½ months of age because of weight loss, vomiting and fever. Physical examination revealed a chronically ill child with irritability, malnutrition,

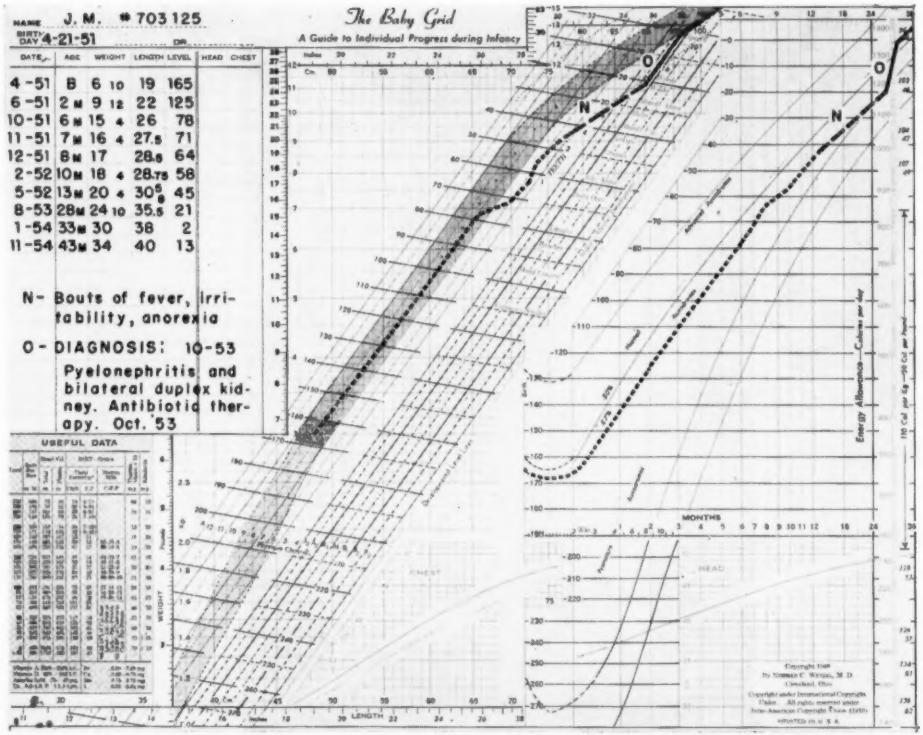
NAME J. M. # 703 125
BIRTH DAY 4-21-51
The Baby Grid
A Guide to Individual Progress during Infancy
DATE AGE WEIGHT LENGTH LEVEL HEAD CHEST
4-51 B 6 10 19 165
6-51 2M 9 12 22 125
10-51 6M 15 4 26 78
11-51 7M 16 4 27.5 71
12-51 8M 17 28.5 64
2-52 10M 18 4 28.75 58
5-52 13M 20 4 30 45
8-53 28M 24 10 35.5 21
1-54 33M 30 38 2
11-54 43M 34 40 13
N- Bouts of fever, irritability, anorexia
O- DIAGNOSIS: 10-53
Pyelonephritis and bilateral duplex kidney. Antibiotic therapy. Oct. '53
USEFUL DATA
MONTHS
HEAD
CHEST
WEIGHT
LENGTH

Fig. 75. Growth pattern of patient J.M. as outlined on the Wetzel baby grid.

hypertension of 150/72. It was not until his second hospital day that abdominal palpation revealed the bladder to be distended to the umbilicus. The left kidney was easily palpated, and a third abdominal mass medial to the kidney, thought to be a palpable left hydroureter, was present. Laboratory findings revealed a blood urea of 150 mg. per 100 ml., plasma carbon dioxide of 17.2 mEq. per liter. The remaining electrolytes were not markedly abnormal. Urinalyses on repeated occasions revealed specific gravities of 1.002 to 1.003, trace of albumin and variable degrees of pyuria. Urine culture yielded *E. coli, Micrococcus pyogenes* albus and *Streptococcus fecalis* on various occasions. Residual urines were 190 cc. and 300 cc. on two attempts. A profound hypochromic anemia was present.

Three days after the infant's admission to the hospital a cystogram revealed a large irregular bladder with a marked reflux up a tortuous large right ureter and a severe hydronephrosis on the right. There was no evidence of filling of the left ureter or left kidney (Fig. 76, A). A suprapubic cystostomy was performed.

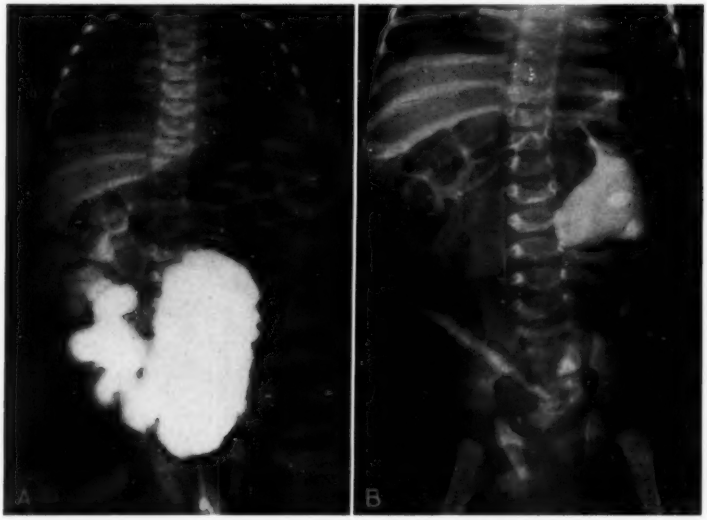

Fig. 76. A, Cystogram done on patient R.C. on his third hospital day at age 6½ months. *B*, Roentgenogram taken after injection of pelvis of left kidney of patient on fifteenth hospital day.

On his fourteenth hospital day a cystogram, performed through the suprapubic catheter, demonstrated still a large irregular bladder, urethral obstruction and bilateral hydroureters.

On the fifteenth hospital day, under local anesthesia, the pelvis of the left kidney was injected with radiopaque material through a needle in the left flank. Roentgenograms revealed marked dilatation of the pelvis of the left kidney with little renal parenchyma visible. A tortuous large left ureter was also demonstrated (Fig. 76, *B*).

The infant's hospital course was characterized by repeated vomiting and azotemia, responding poorly to intravenous therapy. Roentgenograms of the skull, chest and bones were normal. Antibiotics and small multiple blood transfusions were given. The child expired in renal failure on his forty-eighth hospital day. Figure 77 illustrates this patient's growth curve on the Wetzel baby grid.

Postmortem examination revealed a congenital anomaly of the genitourinary system, namely, obstruction of the membranous urethra due to a fibrous ring. There also were

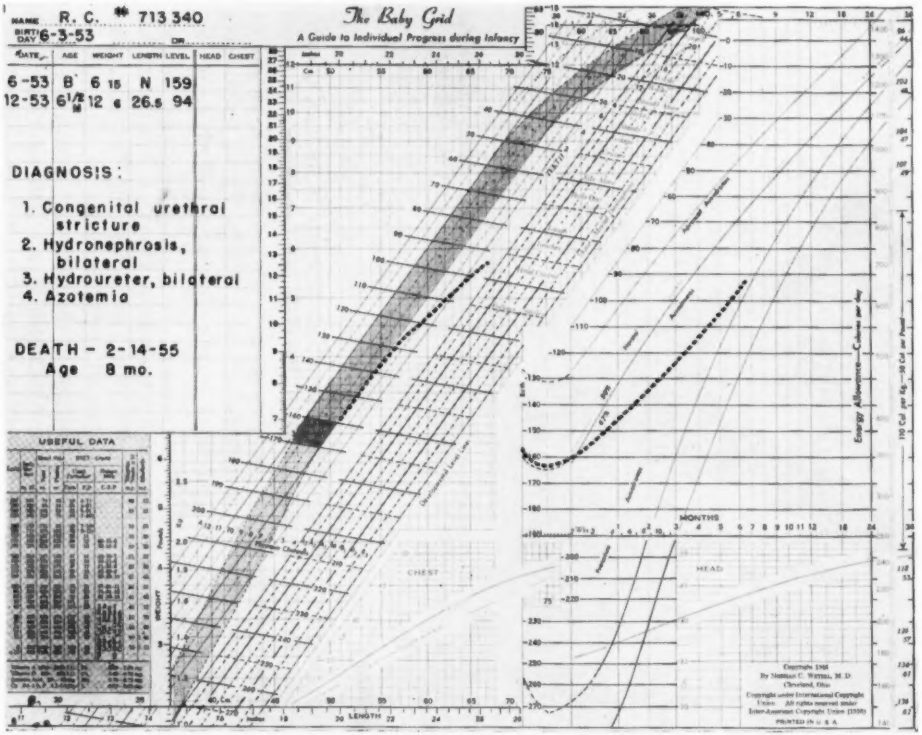

Fig. 77. Growth pattern of patient R.C. as outlined on the Wetzel baby grid.

present bilateral hydroureters, chronic suppurative pyelonephritis of the right kidney, and atrophic pyelonephritis of the left kidney. Figure 78 is a photograph of the urethra, bladder, ureters and kidneys taken at the time of the postmortem examination.

Fig. 78. Pathologic specimen of kidneys, ureters, bladder and urethra removed at postmortem examination of patient R.C. Arrow indicates point of obstruction in urethra.

SUMMARY

In considering the problem of growth failure due to urologic disease, the clinician usually thinks only of the child with extensive and severe congenital anomalies of the urinary tract which create the picture of renal insufficiency, renal acidosis and renal rickets. When severe renal insufficiency exists, the prognosis is poor, and usually death results before adulthood is attained.

The authors emphasize the occurrence of growth failure associated with minor congenital anomalies, compatible with life, but influenced by superimposed infection.

Adequate and constant treatment of the infection often will reverse the growth failure and will permit the clinician to offer to the patient a favorable prognosis for growth and life. Case I illustrates well this point. The authors urge clinicians to consider urologic disease, congenital or acquired, as a cause of growth failure in the patients of the pediatric age range.

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ADRENAL DISORDERS OF CHILDHOOD

FRANK HINMAN, JR., M.D.

A technical and somewhat complicated diagram (Fig. 79) may seem hardly fair to the reader as a start for this discussion, but a moment spent now in pondering these chemical interrelations will make the understanding of adrenal hyperfunction much easier.

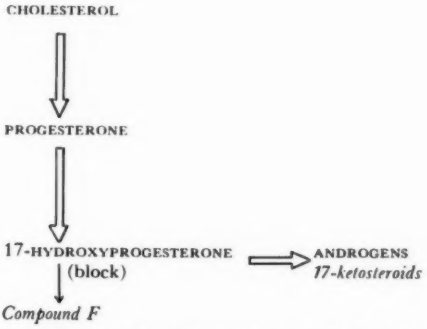

Fig. 79. Steroid metabolism in adrenal hyperplasia. (After Hechter et al.[7]; Jailer[13]; Bongiovanni et al.[2])

The adrenal cortex, according to current concepts, has the principal function of maintaining balance in glucose and protein, as well as salt and water, metabolism. It uses cholesterol as raw material (Fig. 79), converting it to 17-hydroxyprogesterone, and finally to the biologically active substance, *compound F* (hydroxycortisone).[7]

If blockage (probably from inadequate enzymatic activity) occurs in the final conversion to compound F, the 17-hydroxyprogesterone is apparently metabolized to 17-ketosteroids and to *active androgenic substances.*[13]

Observe, then, that this chemical aberration might be expected to have two effects. (1) The excess androgenic excretion would result in masculinization of the female and virilization of the male; and (2) the deficient production of compound F could in certain instances result in the development of Addison's disease. These are exactly the changes found in female children with *pseudohermaphrodism with adrenal hyperplasia* (the so-called adrenogenital syndrome) and in boys with *precocious puberty* due to adrenal hyperplasia (macrogenitosomia precox).

ADRENAL HYPERPLASIA IN FEMALE CHILDREN

The excretion of androgens by the hyperplastic adrenal during fetal life and early childhood produces a characteristic syndrome resulting

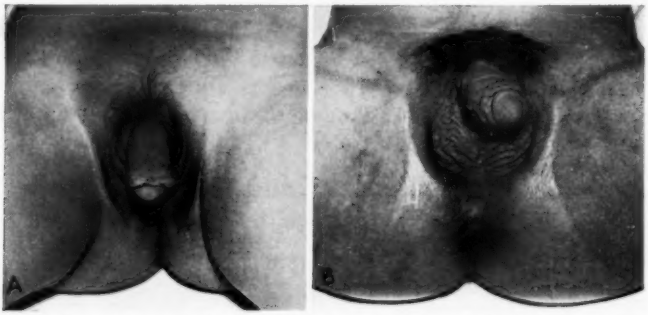

Fig. 80. Three and one-half year old female pseudohermaphrodite, due to adrenal hyperplasia before (*A*) and after (*B*) first-stage hypospadias repair, showing large phallus, partial differentiation of labia into scrotal sacs, and precocious appearance of genital hair.

in the *congenital adrenal intersex*. The term "adrenogenital syndrome," which includes both congenital and acquired adrenal hyperplasia in both male and female, is being superseded by more specific terms.

Experiments on animals show why intersexuality results from early exposure to excess male hormone. The progeny of the opossum, for example, are born in a fetal state developed just enough to cling to the nipples of the mother. If testosterone is rubbed on their abdomens, the females will develop the same intersexual internal and external genitalia as does the human female pseudohermaphrodite with adrenal hyperplasia.

Clinical Findings

The *external genitalia* are intersexual. The girl with congenital adrenal hyperplasia has a large clitoris, which is usually larger than even

a penis would be in a normal boy of the same age (Fig. 80). At the base of the large phallus is the opening to the urogenital sinus (Fig. 81). The urethral meatus thus lies within this cavity, as does the opening to the vagina (Fig. 82). The *internal genitalia* are of normal female configuration, although their development may be somewhat suppressed.

Growth is always accelerated. The child in Figure 80, aged three

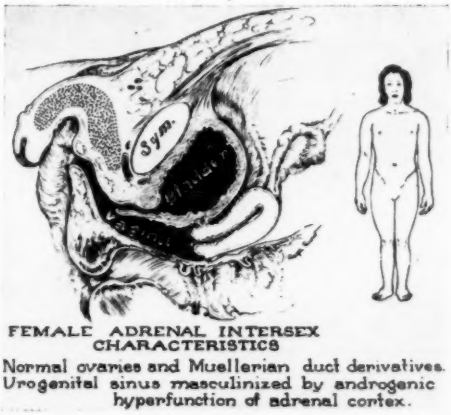
Sym.
FEMALE ADRENAL INTERSEX CHARACTERISTICS
Normal ovaries and Muellerian duct derivatives.
Urogenital sinus masculinized by androgenic hyperfunction of adrenal cortex.

Fig. 81. Diagram of external and internal genitalia of female pseudohermaphrodite. Note hypospadic urethra which opens into common urogenital sinus. (From Howard.[12])

Fig. 82. Fig. 83.

Fig. 82. Simultaneous air cystogram and Skiodan vaginogram in 3½ year old female adrenal intersex.

Fig. 83. Three and a half year old female pseudohermaphrodite showing growth and male habitus.

and one-half years, had a bone age of 12 years. Without treatment the epiphyses close too soon, so that in the end these children are short in stature. Muscular growth is hastened, too, so that the *body contour* is more masculine than feminine (Fig. 83).

The *secondary sex characteristics* of genital hair growth and voice change develop precociously because of the excess androgen secretion. These effects are in part reversible with proper treatment.

Adrenal insufficiency,[3] because of the diversion of adrenal cholesterol metabolism away from cortisone formation toward excess androgen production, is not unusual in the adrenal intersex. Note the pigmentation of the labia and perianal regions in the child shown in Figure 80. This patient has always required supplementary desoxycorticosterone or cortisone, and went into Addisonian crises after the first hypospadias repair.

Laboratory Findings

The 17-ketosteroid excretion, reflecting androgen overproduction by the adrenal, would be expected to be increased. In one of our children, when she was three and one-half years of age, the excretion of 17-ketosteroids was 25.9 mg. per 24 hours. Conversely, the compound F excretion should be decreased. This has been true not only by laboratory measurement. The clinical course of adrenal insufficiency points up the fact of low compound F production.

Differential Diagnosis

The diagnosis problem in congenital adrenal intersexes is to differentiate them from other forms of intersexuality.[12] Actually, the problem is not difficult, for two reasons (1) The frequency of the adrenogenital syndrome is much greater than that of any other form of intersexuality. (2) The child with congenital adrenal syndrome has other physical stigmata of progressive excessive androgen formation, such as precocious development of sexual hair and advanced bone age, as well as abnormally high 17-ketosteroid excretion. Consequently, in children two years of age or older, attention to these points will lead directly to the correct diagnosis. Postnatal virilization from adrenal tumor may be confusing, but is not accompanied by abnormalities of the genitalia (urogenital sinus).

In newborn infants, when the parents are most anxious to know the sex of the child, the physician must use less definite evidence. The baby will have a large phallus with the opening at the base (Fig. 84). This could represent either extreme hypospadias in a male child or a large clitoris. The labia look less like a divided male scrotum and con-

tain no testes. A prostate cannot be felt on rectal palpation, but often a small uterus can. Chromosome differentiation on skin biopsy has been useful in distinguishing sex in these younger children. It is probable that surgical exploration is never warranted, especially since it

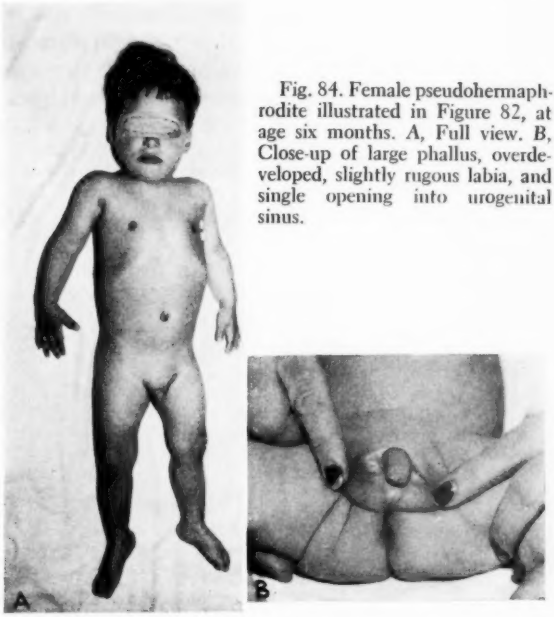

Fig. 84. Female pseudohermaphrodite illustrated in Figure 82, at age six months. *A*, Full view. *B*, Close-up of large phallus, overdeveloped, slightly rugous labia, and single opening into urogenital sinus.

carries an increased risk in these children because of associated adrenal insufficiency.

Treatment

Five years ago it seemed that these children were doomed to the lives of misfits no matter what treatment was used.[8, 9] If they were raised as girls, they would grow into stocky, hirsute young women, with deep voices (Fig. 85). Female breasts could be developed with estrogens, but the patients would remain sterile. If raised as boys, they likewise would be sterile and would be short in stature, but by appropriate plastic surgery on the external genitalia (Fig. 80, *B*), they would make a reasonable adjustment. One of the two children so treated is now eight years old. "He" urinates normally and has the external characteristics of a boy. Even though he is short, his parents are appreciative of his progress and feel that they made the right choice.

However, in 1950, Lawson Wilkins and his associates[18] first reported

suppression of the adrenal hypersecretion of androgens by cortisone. Ordinarily, ACTH stimulates the adrenal cortex to produce cortisone, or compound F; the compound F in turn inhibits ACTH production, so that a balance is maintained. In patients with adrenal hyperplasia, androgen rather than compound F is the product of the adrenal, and androgens have little or no suppressive action on ACTH secretion. Consequently, more ACTH is secreted, which stimulates the adrenal to more androgen secretion. Cortisone administered to the patient substitutes for the lack of her own adrenal cortisone secretion, suppresses

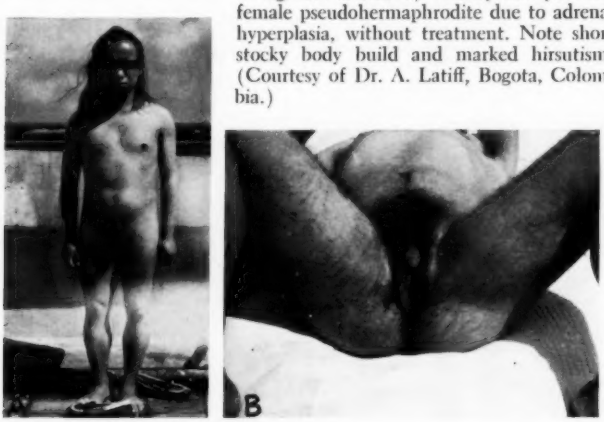

Fig. 85. *A* and *B*, Twenty-four year old female pseudohermaphrodite due to adrenal hyperplasia, without treatment. Note short stocky body build and marked hirsutism. (Courtesy of Dr. A. Latiff, Bogota, Colombia.)

the pituitary ACTH production, and so decreases the formation of androgen.

The amount of cortisone required depends on the individual patient's requirements and on the route of administration.

Individual cortisone requirements for suppression vary considerably. Two siblings aged 13 and 15 under treatment at present, have basal 17-ketosteroid excretions of 19.3 mg. and 22.6 mg. per 24 hours respectively. Given intramuscular cortisone, 50 mg. twice a week, the younger child's 17-ketosteroid excretion fell to 6.3 mg. per 24 hours, while the older child's excretion fell only to 15 mg.

The average dose of cortisone is 25 mg. a day intramuscularly, usually administered in double doses every other day.

Route of administration is important. Cortisone gives a more constant blood level when given intramuscularly, which requires daily or biweekly injection. Oral cortisone, even though given daily in four divided doses, produces sharp rises and falls in circulating levels, which less effectively suppress the pituitary secretion. One of our patients had mild Cushing's syndrome as a side effect of oral dosage. In general,

larger doses of oral cortisone are required than when given by the intramuscular route. However, Goldberg[6] at this institution has had therapeutic results from oral administration in three patients (Fig. 86), in whom breast development progressed and menses began. We are experimenting with longer-acting preparations which can be given at intervals of one to two weeks. This would make the treatment much less traumatic to the children.

Adrenal insufficiency is rarely still a problem after proper regulation with cortisone, but desoxycorticosterone acetate may be given in addition. Especial attention must be paid to electrolyte balance during and after surgical procedures on these children.

TUMOR CAUSING "ADRENOGENITAL" SYNDROME

Wilkins[16] stated that up to the age of ten or 12 years acquired virilization is always due to tumor of the adrenal rather than to hyperplasia. Since the secretion by the tumor begins after fetal differentiation of the urogenital apparatus, the common opening of urethra and vagina will not be present. The orifices will be separate and in normal position. In addition, the secretion of the tumor is usually greater than that from hyperplasia. The virilizing changes come on quickly and often are extreme. The clitoris enlarges very fast, and the 17-ketosteroid level is often, but not always, higher than that usually found with adrenal hyperplasia.

The localization and *treatment* of adrenal tumors, discussed in greater detail in the section on Cushing's Syndrome, aims at complete excision of the tumor.[10] Postoperative hormonal imbalance is not to be expected, since the excessive secretion from the tumor is androgenic, and so usually does not suppress pituitary ACTH production, which would in turn cause contralateral adrenal atrophy.

Fig. 86. Twenty-one year old girl with adrenal hyperplasia after administration of oral cortisone for two months. (Courtesy of Dr. M. B. Goldberg, University of California School of Medicine.)

ADRENAL HYPERPLASIA IN MALE CHILDREN

While at Hopkins, I attended the clinicopathologic conference at which the first case of macrogenitosomia precox due

to adrenal hyperplasia was discussed (later reported by Wilkins, Fleischmann and Howard[15]). Since that time the syndrome is much more frequently recognized.

The disorder has several identifying characteristics. First, the disease is often *familial* (cf. the recent review of this aspect from the University of California Hospital[1]). Many case reports of female pseudohermaphrodites due to the adrenogenital syndrome contain the note that an older (or younger) sibling died of "pyloric stenosis." If details are given, the clinical picture in these infants (vomiting, dehydration,

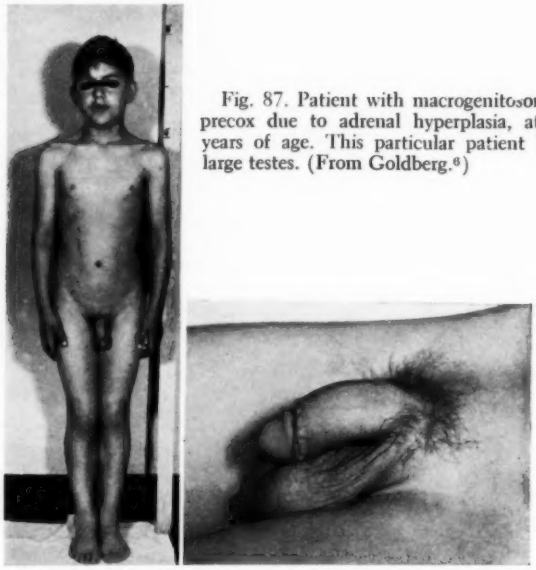

Fig. 87. Patient with macrogenitosomia precox due to adrenal hyperplasia, at 6 years of age. This particular patient had large testes. (From Goldberg.[6])

shock and so on) is indistinguishable from that of acute adrenal insufficiency.

Second, the anatomic changes are typical of *excessive androgen* administration in males ("infant Hercules") (Fig. 87). There is great development of the penis and prostate gland and precocious appearance of sexual hair. The muscular development is advanced, as is the bone age. The voice may or may not be deepened.

Third, there may be *adrenal insufficiency*. Wilkins' patient had an abnormal craving for salt, and when excess salt was not available to him in the hospital, he died of adrenal insufficiency.

At autopsy these children have *hyperplastic adrenal glands*. Usually the testes are small, although in Wilkins' case they were large and filled with "adrenal cells." Other workers have reported Leydig cell clumps

in association with adrenal hyperplasia. In contrast, Goldberg's[6] patient at this Clinic had normal-sized testes, which were histologically mature, in agreement with the skeletal age.

Differential Diagnosis

The premature penile growth usually takes several years to become evident, but after that masculinization is rapid. However, sexual maturation is usually not accompanied by the normal increase in size of the testes (although there are exceptions[6, 15]).

Adrenal tumor causing sexual precocity is rare. It is the most difficult disorder to differentiate from adrenal hyperplasia. If adrenal insufficiency is present, tumor is unlikely. The same is true if a sibling has stigmata of adrenal hyperplasia. The 17-ketosteroid level is often much higher with tumor than with hyperplasia. X-ray visualization of the adrenals or surgical exploration will be required in doubtful cases.

Interstitial cell tumors of the testis, which produce testosterone, are distinguished by local palpation of the testis. Of 20 reported cases in children, all but one had virilization.

Idiopathic precocious puberty, or that due to a hypothalamic lesion, will result in normal-sized testes with normal spermatogenesis—in contrast to the usually small testes with adrenal hyperplasia. Also, adrenal insufficiency will not be present.

Treatment

Therapy, aimed at suppression of adrenal hyperactivity, does not differ from that for female pseudohermaphrodism due to adrenal hyperplasia.

CUSHING'S SYNDROME

That Cushing's syndrome is brought about by oversecretion by the adrenal of 11-oxysteroids (cortisone or hydrocortisone) has been amply demonstrated. Already mentioned is one of our own patients, a 17 year old girl with the adrenogenital syndrome who had hypertension and a moon-face while receiving relatively large doses of cortisone orally. The stigmata of Cushing's syndrome disappeared when the medication was stopped. The classic experimental example of the action of cortisone is the 11 week old female pseudohermaphrodite treated by Wilkins.[18] He noted that she retained sodium and became somewhat obese, and he could see the face become "definitely round with increase in fat pads, so that it resembled somewhat the facies of Cushing's syndrome, although it is not ruddy."

What factor causes the adrenal to oversecrete usually cannot be determined. It may be a basophile adenoma of the pituitary releasing abnormal amounts of ACTH, as originally postulated by Harvey Cushing. Behind this lies the possibility of a hypothalamic disorder which sets the whole chain in motion. In children the problem is simplified by the observation that Cushing's syndrome coming on after birth and before the age of ten years is almost always due to tumor.[17]

Symptoms and Signs

The clinical findings in children with Cushing's syndrome differ little from those in adults. The 11-oxycorticosteroids and the androgens, in proportions varying from case to case, are responsible for the changes in the patient.

The 11-oxycorticosteroids produce a decrease in protein metabolism, by diverting the metabolic stream to glucogenesis. The result is muscular weakness and atrophy, and retarded growth which ends in short stature. The skeleton, laid down in a protein matrix, is consequently incomplete in volume, radiolucent, and subject to fracture. The calcium excretion from demineralization may be great enough to produce renal calculi. The skin is thin and friable. Fat is laid down abnormally (buffalo hump and moon face). Because of the metabolic diversion, the patient may have a glucose tolerance curve like the diabetic and may be resistant to insulin. Hypertension is often present, probably because of the retention of salt.

Androgens are excessive in almost all cases of Cushing's syndrome in children, in greater or less degree, as seen by the hirsutism and acne. Even very young children will have pubic hair. In older girls, since ovarian estrogen excretion is suppressed, amenorrhea occurs. Often the clitoris is large and the female secondary sex characteristics (breast and vaginal growth) are suppressed, in contrast to the advanced state of genital hair growth. In boys the androgens bring about precocious sex development, although to a less degree than in the adrenogenital syndrome. All the 19 cases of Cushing's syndrome from tumor reviewed by us[16] had hirsutism, and all but six had phallic hypertrophy and other androgenic stigmata.

Laboratory Findings

Measurement of the 11-oxycorticoids and the 17-ketosteroids in carefully collected 24-hour specimens of urine, while expected to reveal elevation of both, is often disappointing, probably because of our presently inadequate techniques. High levels are often associated with adrenal tumors, in contrast to the more moderate elevations occurring

with bilateral hyperplasia. Stimulation by ACTH will sometimes, but not uniformly, cause a greater rise in patients with hyperplasia than in normal persons.

Though an abnormal glucose tolerance curve and glycosuria are helpful in the diagnosis, they are not necessary. Only seven of 19 cases of Cushing's syndrome in children caused by tumor had either an abnormal glucose tolerance curve or frank diabetes mellitus.[14] Osteoporosis, when present, is extremely valuable for diagnosis in this age group.

Treatment

Since tumor is almost invariably the cause of Cushing's syndrome in children, treatment must be directed at localizing the lesion and removing it. Plain films and intravenous urograms may visualize the tumor. However, the age of the patient is no contraindication to *presacral gas insufflation;* in fact, the best outlines of the adrenals have been secured in children. If the tumor can be so localized, the problem of surgical excision is simplified.

If, on the other hand, differentiation between tumor and hyperplasia cannot be made, exploration is done (in our opinion usually best carried out through a high transcostal flank incision,[10] but in children the adrenal areas are more accessible transperitoneally than in adults, and that approach may be valuable). If a *hyperplastic* adrenal is found, one can assume that a similar adrenal lies on the other side. This is also true if an apparently normal adrenal gland is found.

Accordingly, the first stage of a subtotal adrenalectomy is done. This consists in excision of four-fifths of the hyperplastic adrenal, planning to remove all the contralateral adrenal at the same or a later operation, through a second flank incision. One-tenth of the adrenal tissue is left behind, which may be enough to support life, with or without supplementary cortisone. Since the remnant may hypertrophy and again cause the disease, removal of all adrenal tissue may be done. This assures the surgeon of cure of the disease, but places a greater burden on the physician for complete and continuous replacement by medication.

If a small or *atrophic adrenal* is found, a tumor probably is present on the opposite side. The small adrenal is not disturbed, and at the same or a later operation the tumor is excised.

If a *tumor* is found on the first side, one can be sure that the opposite adrenal is functionally atrophic, so that vigorous replacement therapy will be necessary during and after operation. We found the mortality from acute adrenal insufficiency very high before cortisone was available,[5, 14] but with proper preparation[11] the deaths from the operation can be greatly reduced.

SUMMARY

In congenital adrenal hyperplasia, adrenal steroid metabolism is diverted from the pathway of compound F production to androgen formation. Since this occurs during fetal life, the female infant has intersexual genitalia from the androgens and may have adrenal insufficiency from inadequate compound F. Precocious puberty results in the male child. Cortisone given orally or intramuscularly opposes pituitary ACTH secretion and so reduces androgen output, at the same time that it makes up for the deficit in compound F.

Cushing's syndrome, on the other hand, is caused by oversecretion of adrenal corticoids. In children it is usually due to tumor, which must be located and excised, despite the danger of postoperative adrenal insufficiency.

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CHILDHOOD NEPHROSIS

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Nephrosis, which from its Greek derivation means "a condition of the kidney," is a term so widely used in connection with kidney disease that it is necessary to define our use of it here. In pediatrics it has come to mean almost exclusively an idiopathic "nephrotic syndrome" or "nephrotic state" having its onset usually in early childhood, and characterized by anasarca, massive proteinuria, hypoproteinemia and hyperlipemia.

In the past it was customary to subdivide this syndrome into two categories: "pure lipoid nephrosis" and "the nephrotic stage of chronic glomerulonephritis." Though this condition often does progress to renal failure and a picture of chronic nephritis, we have seen no convincing evidence that the nephrosis is a phase of a pre-existing classical chronic nephritis. Furthermore, the terms "pure" or "lipoid" nephrosis are not acceptable on the grounds that, in the first instance, the pathogenesis is too obscure to justify any assumption of purity, and that, in the second instance, the nephrotic syndrome due to any cause may show "lipoid" features with hyperlipemia and lipoid deposits in the tubules.[3] Thus it seems desirable to call this condition "childhood nephrosis" or more simply "nephrosis"—because this broader term has no pathogenetic implication and embraces the whole idiopathic syndrome.

INCIDENCE

Childhood nephrosis usually has its onset between 18 months and four years of age (Fig. 88), though it has been reported in the newborn period[33] and occasionally begins in later childhood and adult life. It

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occurs more frequently in boys. In a recent cooperative study* (Table 10) of 534 cases, 66.2 per cent were in males. There has been no detectable racial or climatic predominance. The appearance of a second case in a family has been roughly estimated as happening in 2 to 3 per cent of cases[44] higher than its incidence in the general population, but still suggesting no more than perhaps a familial diathesis.

The exact incidence of the disease is not known, but we have made a rough calculation based on mortality figures for New York City com-

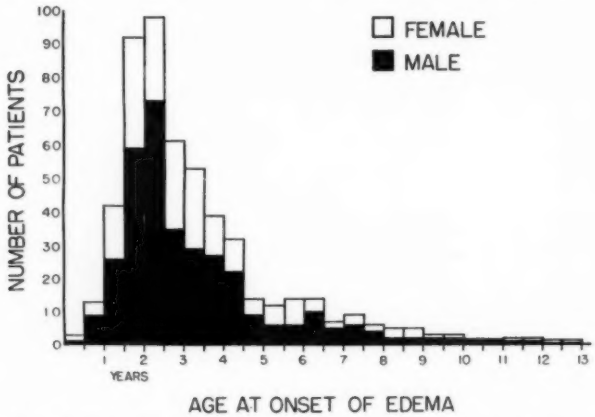

Fig. 88. Distribution of 534 cases of childhood nephrosis by age and sex at time of onset of edema.

bined with the survival rates demonstrated in the cooperative study mentioned. From this an incidence of less than one new case in a child under ten years per 100,000 total (adult and child) population each year is suggested.

ETIOLOGY

Since we have already considered this to be "idiopathic" it is obvious that the cause of this condition is unknown. Certain possible causal factors have been considered and found wanting. Infection, notably the pneumococcus as suggested by Blackman,[12] has not been established as a cause. Since it occurs in all economic levels, dietary factors would not seem to be important. The possibility of a genetic factor is raised by the familial incidence, but this at most can play only a contributing role. The incidence of classical allergic manifestations in these children is high, but not enough greater than in the general population to have any statistical significance. The possibility that childhood nephrosis

* Supported by the National Nephrosis Foundation, Inc.

TABLE 10. *Sources of Cases Used in Evaluating Adrenocortical Active Hormone Therapy in Childhood Nephrosis*

REPORTING PHYSICIAN	LOCATION	NUMBER OF CASES
Clark West	Cincinnati	37
Conrad Riley	New York City	112
A. J. Merrill	Atlanta	10
W. W. McCrory	Philadelphia	58
M. Frances McCall	Montreal	40
Henry Barnett	New York City	95
Kurt Lange	New York City	44
Walter Heymann	Cleveland	97
Lawrence Greenman	Pittsburgh	41
		534

represents some kind of abnormal antigen-antibody reaction is being given serious consideration by research workers, though definite evidence concerning this is still lacking. Lastly, a question often raised by parents is whether psychologic factors play a role; there is no evidence to suggest that this is so.

PATHOLOGY

Early in this century Munk[42] and Volhard and Fahr[54] studied the renal histopathology of nephrosis and found only degenerative tubular lesions, the most prominent feature of which was lipoid deposition in the epithelial cells. Consequent to these descriptions, there was thought to exist a distinct entity called "pure lipoid nephrosis," which was differentiated clinically from chronic nephritis by the absence of hematuria and nitrogen retention and pathologically by the absence of glomerular changes, at least with hematoxylin and eosin stain.

Later, better elucidation of normal renal physiology followed by renal function studies in nephrosis suggested that there must be glomerular as well as tubular involvement. Since antibiotics have been available, most children with nephrosis have survived their intercurrent infections and had a more prolonged course. At present, cases of nephrosis coming to autopsy usually show glomerular lesions which are apparent with hematoxylin and eosin stain. Changes in the basement membranes are consistently found, often accompanied by swelling and proliferation of the epithelial cells. In some cases there are also adhesions of the glomerular tuft and crescent formation, which may be interpreted as evidence of superimposed glomerulonephritis. There may be extensive fibrosis of the interstitial tissue with mild lymphocytic infiltration. Complete obliteration of glomeruli with hyalinization may occur. The severity of the damage is roughly but not absolutely correlated with the chronicity of the disease and with the degree of impairment of renal function. Furthermore, in a re-examination of nephrotic kidneys in

which no significant glomerular lesions could be seen with hematoxylin and eosin stain, Bell,[11] Ellis[20] and Ehrich et al.[19] were able, by using newly developed stains, to find splitting and thickening of the basement membrane of the glomerular tufts.

The original concept of pure lipoid nephrosis without glomerular pathology has, therefore, been discarded by most investigators in favor of the belief that the tubular changes found in nephrosis are secondary in importance to the less conspicuous but nevertheless demonstrable glomerular damage. An extensive review and interpretation of the pathology of the nephrotic syndrome has recently been published.[3] The pathogenesis of the functional and morphologic abnormalities of the glomerulus continues to be a matter for speculation.

RESEARCH

This discussion is prepared primarily from the clinical viewpoint, and no attempt can be made to review in detail the research being done on the disease. There are good reviews and symposia available which may be consulted.[3, 8, 13, 52]

Here we can mention only the general current lines of approach. In late years renal function has been investigated extensively and is referred to under Laboratory Findings. Electrolyte distribution is being carefully explored.

A promising approach is the production of a nephrotic syndrome in experimental animals. The most widely used method for this purpose is the administration of a nephrotoxic serum produced by stimulating antibody production in one species (e.g., rabbit) against the kidney of another species (e.g., rat). The injection of a serum containing such antibodies into the species against which the antibodies have been developed will regularly produce an obvious nephritis, and with the rat specifically, if the dose is great enough, a nephrotic syndrome.[28] A nephrotic syndrome can be produced in hamsters by infecting them with Leishmania.[24] The introduction of a mouse sarcoma into gonadectomized hamsters will produce similar results.[1] These latter conditions are associated with amyloid deposition in the kidneys. Such experimental nephrosis may help to find what is common to the syndrome resulting from different causes.

In human beings many studies as to the nature of protein disturbances have been conducted. The original hypothesis of production of abnormal protein has not been borne out.[25, 26] Recently changes in serum complement level have been explored. The thought that nephrosis could result from an antigen-antibody combination was given impetus by the experimental use of nephrotoxic serums in animals. With this in mind, Lange's report of the low complement level in sick nephrotics which returns to normal or higher in remission suggested to him that the cessation of antigen-antibody combination freed complement in human beings.[17, 34, 36] The question of the loss of complement in the urine, and the technical problems of complement measurement, make the hypothesis still only tentative.

Because of the evidence suggesting extrarenal metabolic dysfunction in nephrosis, there is still diversity of opinion as to whether it is strictly a disease of the kidney or whether it is more widespread, possibly a general disturbance of capillary function, with involvement of the kidney but a part of the total picture. The answer to this question will have to await more exact understanding of the pathogenesis of the disease.

CLINICAL PICTURE

The onset is usually insidious in a previously healthy young child. The parents first notice puffiness of the eyes and later swelling of the

ankles and abdomen. If queried, they will often have recognized that the child's appetite has declined. It is not unusual for the edema first to be noticed after a "cold," and it is certainly true that a known nephrotic patient in quiescent phase will frequently suffer relapse after such infection. More often there is no recognized antecedent infection.

The anasarca may grow progressively worse, may reach a static state, or may spontaneously regress. Some patients whose early course was characterized by frequent spontaneous remissions and relapses have subsequently settled into an unremitting state of anasarca. The course is thus very variable.

The duration of the disease is also variable. A few cases have been seen with edema only for a month or two, then remission and gradual clearing of abnormal laboratory findings. More often the condition persists for 18 to 30 months, and occasionally it lasts in an active state four or five years or even longer.

The commonest complication is infection: peritonitis, cellulitis (erysipeloid), pneumonia, and the like, all of which are frequently associated with bacteremia. In the days before adequate antibacterial therapy these often were the cause of death, but now are usually readily controlled with early treatment. Though the pneumococcus predominates as the infecting organism, *Escherichia coli* and other pyogenic bacteria are implicated often enough so that a broad-spectrum antibacterial agent should always be used until the culpable organism can be identified.

Diarrhea, not adequately explained, but thought to be due to poor absorption by the edematous gut, is not unusual. This is an annoying complication, but seldom produces serious electrolyte imbalance.

Skin rashes, perhaps due to monilia or other parasitic infections, are not uncommon. Intertrigo may cause concern, but can be controlled by good skin hygiene. The edema of the scrotum and penis frequently upsets parents, but fortunately, despite the appearance, does not compromise normal micturition.

Another not uncommon complication is the development of hernia, inguinal or umbilical, as the abdomen becomes distended with fluid. Rarely a hernia becomes incarcerated and requires surgical intervention, which has, in our experience, been well tolerated. Usually, however, the hernia needs no treatment, and can be repaired after the patient has recovered from his nephrosis.

LABORATORY FINDINGS

Early in the course of nephrosis there are three characteristic laboratory findings: (1) Massive *proteinuria*—in the first weeks this occasionally is variable so that some urine specimens may show little or no

protein; but once the disease is well established, this becomes a consistent finding, showing a 4+ qualitative test for protein most of the time. The protein in the urine shows a preponderance of albumin.[38, 51] Microscopic examination shows casts—hyaline, fine and coarsely granular. (2) Marked *hypoproteinemia*—this tends to affect the albumin more than the globulin, so that there is a reversal of the albumin-globulin ratio.[38, 51] The serum albumin has been found by immunochemical techniques to be as low as 0.1 gm. per 100 ml.,[25] though by the usual techniques (Howe fractionation) it is reported as being 0.8 to 2.0. Gamma globulin is also markedly depressed. (3) *Hyperlipemia*—this is shown both by visible lipemia (milky serum) and a markedly elevated total serum cholesterol (600 to 1000 mg. per 100 ml.). Total fats are also elevated, but not usually measured. The increase is mostly in the neutral fats.[43] Many of these are undoubtedly bound to protein, as shown by the high beta-lipoprotein fraction.[10]

Other abnormalities which may occur early, and which have given rise to the discussion of whether this condition frequently represents a form of chronic glomerulonephritis, are hematuria and nitrogen retention. Most patients with childhood nephrosis show only a slight degree of hematuria—in rough clinical tests up to 2 to 4 red blood cells per high power field in a centrifuged sediment. More marked hematuria is cause for some concern, since, in general, patients who pass significant amounts of blood seem to fare less well than those who do not. It is important to remember, however, that there are many exceptions to this generalization, even though the hematuria be gross. Thus hematuria, regardless of degree, is not of absolute value as a prognostic sign.[4] White blood cells also are not infrequently present in the urine, but unless clumped and present in large numbers, do not seem to indicate urinary tract infection.

Nitrogen retention can be an ominous sign, but frequently is seen transiently in patients who eventually recover. In following the course of the disease this evidence of loss of renal function may be the earliest sign of serious trouble; hence some suitable test such as the level of nonprotein nitrogen of blood or of blood urea nitrogen should be done at intervals. It is important to remember that a single elevated reading is not necessarily significant. Steadily rising nitrogen levels over a period of two to three months usually do imply irreversible renal damage.

Tests of renal function such as urea clearance, inulin clearance, and the like, are done in many clinics.[9] Urea clearance in our hands has proved so unreliable and adds so little to our prognosticating ability that we do not use it. The more elaborate clearance techniques are suitable only for investigative purposes. When these clearance tests have been used, they have shown variability in individual cases, dem-

onstrating that renal function may be temporarily impaired and yet show complete recovery.[14] From the viewpoint of management and prognosis, serum nonprotein nitrogen or blood urea nitrogen determinations are adequate.

Concentrating power of the kidney is not lost early, so that this test of function is of little help. The phenolsulfonphthalein test is so crude that it does not have much place in evaluating progress.

In cases in which irreversible renal impairment has become established, other laboratory tests are useful. Thus, early in renal failure, phosphorus excretion is depressed so that serum concentrations rise as high as 8 to 10 mg. per 100 ml. With the low serum protein to which calcium is bound the total serum calcium even without renal insufficiency is often found to be 7.5 to 8 mg. per 100 ml. With rising phosphorus this falls to still lower levels, and tetany becomes a threat. Also as a sign of renal failure, acidosis may develop, and the measurement of serum concentration of sodium, potassium, chloride and carbon dioxide capacity becomes important for planning management. With renal failure sodium levels in the serum fall as the carbon dioxide capacity falls and chloride rises. Terminally, the level of potassium may rise.

A laboratory test mentioned last because of its nonspecificity is the erythrocyte sedimentation rate. In contrast to rheumatic fever or acute bacterial infection, the usual concept of nephrosis does not suggest an inflammatory process. Nevertheless, in the full-blown nephrotic state the sedimentation rate is characteristically elevated—higher, actually, than in any other condition of childhood. It is probable that the elevation of the sedimentation rate is on a different basis than in the inflammatory diseases, and may represent the combined effect of a number of chemical aberrations. Despite its nonspecificity, however, it is proving a useful guide in following the course of the disease (see Hormone Therapy).

DIAGNOSIS

Diagnosis of childhood nephrosis is not difficult. First, the nephrotic syndrome as such must be separated from other conditions giving rise to anasarca. Chronic heart failure and cirrhosis of the liver can occur in childhood, but are rare. Allergic swelling of the eyes may call for differentiation. The finding of massive proteinuria, hypoproteinemia and hypercholesterolemia promptly identifies the anasarca as arising from the nephrotic state.

Secondly, other causes of the nephrotic syndrome must be ruled out. Such causes known in adults are the Kimmelstiel-Wilson syndrome,[30] amyloidosis of the kidney[23] and disseminated lupus erythematosus[2];

of these only the last can be expected, though rarely, in childhood. The syndrome can be seen with syphilis[23] and frequently other infections, any of which should be identified with ease. Renal vein thrombosis has been reported to give rise to nephrosis, but is rare as a cause.[18] Idiosyncrasy to drugs such as trimethadione,[5] para-methadione[55] and gold[53] must be considered. Lastly, chronic glomerulonephritis as a cause is thought to be frequent in adults, but well documented cases of pre-existing chronic nephritis before the appearance of the nephrotic state are rare. We have never seen such an instance in a child, though we have been told of an occasional case by competent observers. In general, however, the occurrence of the nephrotic syndrome in a child can be confidently considered idiopathic "childhood nephrosis," though the possibility of these other causes must be borne in mind.

OUTCOME PRIOR TO ADRENOCORTICAL ACTIVE HORMONE THERAPY

The outcome in an individual case cannot be predicted early. If "cure" is to result, we feel confident in proclaiming it only after a period of six months to a year has elapsed with completely normal laboratory findings. Even after this a rare recurrence has been known. It is possible that current treatment may make an even longer period necessary. Though a fatal termination may be suspected by certain ominous findings early, there are enough exceptions to any general rules so that an assured prediction of death can be made only when steady deterioration of renal function has been observed over a period of months.

From our experience at Babies Hospital plus the combined experience previously quoted, we can make the approximation that three years after the onset of the disease, without modern treatment, one would expect one third of the patients to have died, one sixth to have progressed to "cure," and the remaining half to be alive, but still showing evidence of their disease. In Figure 89 the percentage of patients surviving in each year after the onset of the disease is represented over a seven year period.

As already mentioned, rare deaths occur as a result of infection. The usual death occurs between 18 and 30 months after onset while the patient is still edematous. Disturbed renal function is apparent, but there is far from complete loss of renal function, as shown by the fact that nitrogen is retained only to a moderate degree, the nonprotein nitrogen of the blood being in the order of 120 to 130 mg. per 100 ml. terminally. Interestingly, there is rarely much blood pressure elevation. The heart, which is usually small in childhood nephrosis,[15] enlarges, and the terminal event appears to be cardiac failure. A pericardial

friction rub is occasionally heard. Digitalis may produce transient and short-lived improvement. The exact cause of this final event is not clear.

Rare cases in children duplicate the more usual picture for adults. After some years of anasarca, they lose their edema, show progressively failing kidney function, and progressive anemia requiring transfusion. This phase may last several years. In this group the development of "renal rickets" is not uncommon. Finally, blood pressure rises to high levels, eyeground changes appear, and azotemia increases to extreme degree. Death is often heralded by convulsions.

Other cases progress to clinical recovery in two to three years, but cannot be considered "cures" because they may still show proteinuria

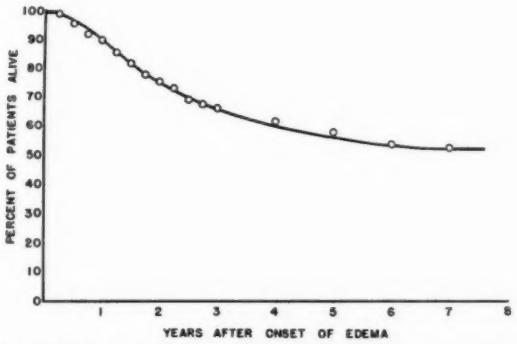

Fig. 89. Cumulative percentage survival during first seven years after onset of nephrosis in patients with no effective adrenocortical active hormone therapy (see text under Treatment). Total number of cases: 429. Average population per year: 115.

of some degree. Some of these cases eventually clear completely, but prediction of the final result is impossible because of the lack of any really long-term studies. Kohn[31] reported two patients with 24 and 25 year follow-ups still alive and clinically well despite persistent proteinuria.

Lastly, there is the group of apparent "cures." This happy state is usually reached after 18 months to two years of disease. Criteria for this have already been defined. Whether such a "cured" patient may in later adult life show signs of reduced renal reserve is not known, because follow-up studies of sufficient duration are not available.

TREATMENT

Management of the Patient

Supportive treatment is a necessary adjunct to specific treatment. Administration of extra vitamins to a child with a capricious appetite

seems like good insurance. Particularly, the treatment of infection, when it appears, is important. Some authors[16] make a practice of giving continuous prophylactic antibiotic such as oxytetracycline (Terramycin). Since we fear the emergence of resistant strains of organisms, we do not do this, but give therapeutic doses of an antibacterial agent at the least sign of fever or even with the common cold. With this regimen the danger of uncontrollable infection is minimized.

For direct attack on the nephrotic syndrome, among the older yet still popular approaches is the use of thyroid extract. The high serum cholesterol, low basal metabolic rate, low protein-bound iodine[46] all make hypothroidism seem like a reasonable part of the picture. It can only be reported that many trials of thyroid administration have proved this approach to be generally ineffectual.

It sounds logical to give a high protein diet to a patient with low serum protein, who is constantly losing protein in the urine. Unfortunately, empirical test has shown that these patients can only utilize a normal protein intake,[22] and the deterrent to adequate caloric intake of a high protein diet may do more harm than good.

The low sodium diet, so effective in cardiac edema and possibly in cirrhotic edema, has, on empirical grounds, been ineffective, and is thought by some to be dangerous because it may produce sodium depletion. In any case, its interference with the capricious appetite of the nephrotic child, in our opinion, has made it inadvisable. As for diet, we have taken the stand that any fare which appeals to the child's appetite is the most useful, with the slight qualification that it is best to avoid excessively salty foods.

The use of diuretics effective in other edematous states has not proved significantly beneficial in nephrosis. The mild xanthine derivatives in general do nothing. The mercurials, though they produce a transient increase in urine volume, usually have such a minor effect as to be valueless. There is, of course, the theoretical objection that they might increase renal damage, but documentary evidence for this is lacking. The use of urea as a diuretic, while sometimes effective, is only palliative. Also, the high blood urea nitrogen level thus produced interferes with one of our measurements of renal function. Acetazoleamide (Diamox) has not in general been useful.

Hyperoncotic plasma substitutes such as concentrated serum albumin, dextran and P.V.P. (polyvinylpyrrolidone) may induce diuresis frequently, but their effect is strictly palliative and often exceedingly transient. Therefore it has been our practice to use them only when all else fails.

Mechanical relief of tension, as by abdominal paracentesis and thoracentesis, are old last-ditch stand-bys. They can afford relief of discomfort and still must be used occasionally. When to use such treatment

depends upon the clinical judgment of the individual doctor. Our own belief is that they should be used to relieve discomfort, and not be saved as last-minute emergency procedures.

The effect of measles and perhaps certain other virus infections on the nephrotic syndrome in children is usually dramatic.[29, 50] Though the mechanism of its operation is not understood, three quarters of edematous patients do have a diuresis following this affliction, and rarely permanent remission results. Though this has been used as therapy, present forms of treatment are good enough so that the risk of measles is no longer justified.

So much for the older forms of popular treatment. Currently, the introduction of corticotropin and various adrenocortical steroids has fortunately made resort to any of the foregoing types of treatment, except the supportive, almost unnecessary.

Hormone Therapy

When corticotropin and cortisone were first made available for clinical use in 1949, it soon became apparent that a transient remission evidenced by rapid diuresis could be induced in nephrotic children in about three out of four tries.[21, 37, 41, 45, 47] Since no immediate measurable change is produced with the administration of either of these hormones, determining the optimum dose for an individual patient is not possible. With experience it has become evident that large doses are necessary, and for the induction of diuresis it is customary to give a two to three year old child 25 units of corticotropin intramuscularly, or 50 mg. of cortisone by mouth every six hours for ten days. Diuresis usually begins eight to 12 days after the beginning of treatment. In our experience there seems to be no great difference in the action of the two agents.[48] The fact that ACTH is given parenterally may assure absorption when this function is possibly disturbed by local intestinal edema.

Initially, this form of treatment was used only for relief of the edematous state. Later, Kramer[32] reported giving a second course when the patient was edema-free; this resulted in considerable improvement in chemical findings. Next Lange,[35] who found that the usually low serum complement of nephrosis appeared to be raised with hormone treatment, reported that this level could be kept high if large doses were given three consecutive days each week. He has reported favorable results over prolonged periods with this regimen.[36] Thus various schemes of "maintenance" therapy have been tried. Merrill[39] has used continuous treatment, we have tried ten consecutive days out of each month, and Greenman et al.[27] have been using 28 consecutive days of treatment. The small groups treated by the separate methods are not

suitable for good statistical evaluation. Therefore in our combined study we have tried to compare only three categories of patients: those who received no hormone therapy, those who received it sporadically to relieve edema, and those who received it according to one of the preplanned schedules. It soon became apparent that there was no significant effect on the ratio of complete "cures" to deaths. On the other hand, it was the impression of all workers that the patients were

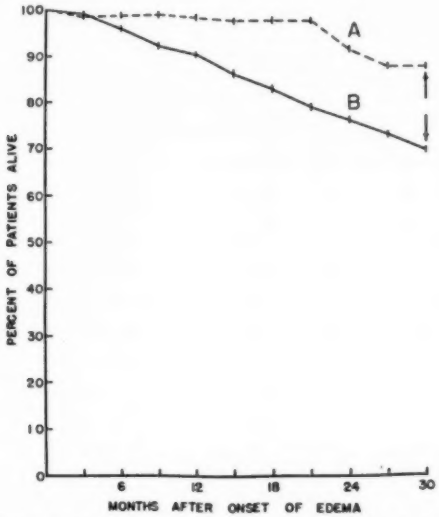

Fig. 90. Cumulative survival curves for patients with childhood nephrosis. Curve A, patients treated by preplanned schedule; based on a total of 123 patients, with an average population of 50 for each three month period. Curve B, patients who received ineffective or no treatment; based on a total of 429 patients, with an average population of 218 for each three month period. For difference in survival at 30 months (arrows), P is less than 0.01.

doing better in general; so another method of evaluation had to be developed.

Accordingly, the results were analyzed by the use of the "life table" technique to determine duration of life after onset of the disease according to the type of treatment. A preliminary report based on 534 cases has been presented.[49] It is hoped that this will be expanded as more reports become available. In this, no detectable difference in survival was noted between patients receiving no hormone and those receiving it for edema only. These two categories were, therefore, pooled to offer a larger group for comparison with the "preplanned schedule" group. Figure 90 shows the survival curves in terms of percentage alive according to time after onset of the disease. As can be seen, there is a sta-

tistically significant smaller number of deaths two and one-half years after onset among the schedule-treated patients than in the other pooled group. The facts that the numbers considered are not large enough, that patients treated early as well as those in whom treatment was begun late are all considered together, and that controls and treated patients are not contemporaneous, mean that the case is by no means proved, though the implication is encouraging.

At this time it is impossible to outline the optimum type of treatment. From the foregoing observations it is suggested that simply to treat edema when it appears is not enough. Any of the suggested schedules is probably better than this.

Rather than blind scheduled treatment, it would be better if there were some measurement to indicate when treatment is necessary. In some patients urinary protein disappears with remission, and many physicians have used its reappearance as an indication to treat again. However, some patients never do clear protein from their urine and so, by this standard, would be treated continuously, which we believe would be unwise. Others have actually been seen to start re-accumulating edema even before they begin to show proteinuria. Therefore we have not felt that this feature was an adequate guide to treatment.

In our Clinic we have been using the erythrocyte sedimentation rate as an index. This is a nonspecific measurement, but empirically we have found that we could anticipate both improvement and relapse by a falling or rising sedimentation rate respectively. For about six months now we have been gauging treatment by this means in place of any fixed regimen, and have so far been impressed that we could foretell and presumably prevent edema. Although it is far too early to say that this is the best method of treatment, at this time, when we are in no position to make a definite therapeutic recommendation, we merely propose it as a feasible method for a practising physician to direct a nephrotic's care.

Our method has been to initiate hormone treatment in the hospital, starting it immediately on diagnosis. We continue treatment, regardless of diuresis, until the sedimentation rate has reached the normal level for whatever method is used, setting a maximum period of time as four weeks. We use doses of corticotropin or cortisone as discussed for the treatment of edema. If the sedimentation rate does not begin to fall after ten to 14 days, we may raise the dose. Usually by the end of three to four weeks this measurement will have dropped to normal. Then we stop treatment and follow up the patient in the clinic with repeated tests, at first at one week intervals, and after one to two months, more infrequently if the rate remains normal. If it begins to rise, we treat again and have been impressed that it falls rapidly to normal if the elevation is not great. With this regimen we have ob-

served that we can keep patients free of edema most of the time. Needless to say, there are distressing exceptions, but in general they do well.

It must be remembered that hormone therapy of this sort is believed to increase the risk of infection. For this reason we always give some antibacterial agent along with the hormone. Usually, we give sulfisoxazole (Gantrisin), approximately 0.1 gm. per kilogram per day, and we discontinue hormone treatment in the presence of infection.

There are other precautions to be borne in mind. Azotemia may increase with hormone administration[7]; hence if such medication is started with any abnormal nitrogen retention, it must be closely supervised. Such treatment may cause lowering of serum potassium; therefore, if treatment is continued beyond two weeks, we give potassium chloride, about 1 gm. daily.

Renal Failure

Lastly, a brief word has to be said about the management of renal failure. This cannot be discussed extensively, and the reader is referred elsewhere for more details.[23, 40]

Usually, the first detectable evidence of progressive kidney deterioration is the loss of the ability to clear urea. With this, control of calcium-phosphorus balance fails (see Laboratory Findings) and tetany may result. Meanwhile, the base-saving function of the kidney is disturbed and acidosis ensues, protecting somewhat against the development of tetany.

Under these conditions one has to hold the line as well as possible. The administration of extra calcium and the attempt to prevent phosphorus absorption by giving aluminum hydroxide gels by mouth may help somewhat to control acidosis[6] and at the same time to prevent tetany.

In this renal failure stage, support by transfusion may help combat the lack of erythropoiesis, which is unaffected by iron administration or other "hematinics."

Finally, as uremia becomes more pronounced and vomiting becomes a feature, chlorpromazine may help symptomatically.

Management of Parents

Almost as important as the treatment of the patient is the management of the parents. With a disease in which the duration is so long, the expense so great and the outcome so uncertain, the parents need a great deal of careful guidance if they are to weather the storm and to bring their child through emotionally healthy as well, we hope, as organically cured.

First, the enormity of the problem may well fill them with feelings of guilt, so that reassurance by the physician that neither their commissions nor omissions have given rise to the disease may give them strength to face the other problems. Secondly, a frank discussion as to current medical knowledge, as well as lack of knowledge, of the nature of the disease reassures them as to the physician's competence. With amazing rapidity they meet friends or go to the library and read books, and return with varying amounts of information and misinformation about the condition. The more of this that can be anticipated, the easier is the direction of therapy. Ideas about diet and the use of thyroid are almost certain to be gleaned from some of their sources. If these have already been discussed, confidence is greater. For these reasons we feel that as soon as we establish the diagnosis, a long and frank conversation with the parents is very rewarding.

In such a conversation it would, of course, be criminal to avoid the serious implications of the condition, but on the other hand, the hopeless outlook which physicians are apt to take is equally unjustified. The realization that, no matter what ominous signs may appear early in the course, the possibility of recovery is still very real, makes the situation much more tolerable and elicits real cooperation from the tormented adults.

An important role which the parents can play in the management of the physical aspects of the disease is to be alert to detect the onset of infection. They should not be unduly frightened by the possibility of such a complication, but they should be respectful of it so that early treatment can be started. They should be taught to respect but not dread the common cold. They should take reasonable precautions to avoid exposure to this infection, but should realize that, though it may precede a set-back, it probably does not imperil the eventual outcome.

Lastly, they must be taught to realize that if the child is pampered because of his invalidism, the damage to his future emotional life, if he survives, can be almost worse than if renal failure overtakes him.

CONCLUSION

In brief summary, the nephrosis of childhood appears to be a distinct clinical entity. The mortality rate is high, but current hormone therapy from a preliminary evaluation appears to be prolonging life. Many patients recover completely without apparent residual renal damage. The criteria for giving a definite prognosis as to whether an individual patient will live or die are very uncertain, so that optimism in dealing with parents is justified until incontrovertible evidence of irreversible renal damage is at hand.

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